

BIOGRAPHICAL SKETCH

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NAME: DEMICHELIS, Francesca

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POSITION TITLE: Professor, University of Trento

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Trento, Trento, I	M.S.	10/1996	Physics
University of Trento, Trento, I	Ph.D.	02/2005	Computer Science/ Computational Biology
Harvard Medical School, Brigham and Women's Hospital, Boston, MA	Postdoctoral Training	10/2007	Cancer Genomics

A. Personal Statement

My laboratory in Computational and Functional Oncology at the University of Trento, Italy, focuses on identifying biomarkers of tumor progression and defining the molecular characterization of lethal subtypes of GU cancers. Building on years of interdisciplinary work on prostate cancer and the understanding of cancer genomics, the laboratory integrates computational and experimental expertise in translational research projects that are laser-focused on open clinical questions. The team includes 15-18 members, funded through competitive grants. On the analytical side, my team developed several approaches to model *in situ* protein heterogeneity, to track tumor dynamics while exploiting single-base resolution data and single allele information, and to detect circulating tumor signals via multiple analytes, with the overall goal of optimizing robust tumor information extraction for biomarker discovery and validation. We made significant contributions to the characterization of prostate and bladder cancer evolution (funded by an ERC-CoG grant, 648670), which translated into pioneering liquid biopsy results concerning AR-targeted therapies and AR-independent prostate cancer epigenetic reprogramming. Long-standing collaborations are in place, including with Weill Cornell Medicine, Harvard University, UCL, and Cedars Sinai, also through my active role in consortia over the years (e.g., MAQC-II, TCGA-PRAD, Stand Up 2 Cancer, SU2C-PCF International Dream Team, and CCG Ancestry Informative Markers AWG (TCGA-NCI) (Nat Biotechnol 2010, Nucleic Acids Res 2010, Cell 2015, Cell 2015, PNAS 2019, Cancer Cell 2020). Since 2018, through an Accelerator Award from CRUK-AIRC on liquid biopsy in collaboration with UCL, we have focused on developing assays integrating cancer genomics and epigenetics from cell-free DNA and transcriptomics from extracellular vesicles while providing protocols and know-how on both pre-analytical-and-analytical steps.

Ongoing and recently completed projects that I would like to highlight include:

NIH R01 CA287075-01A1, MPI (Di Vizio, Stott, Demichelis). 09/01/2024-08/31/2029. Clinical Translation of a Large Oncosome-Based Prostate Cancer Blood Test (PLUS). \$657,000 USD to Demichelis.

Italian Foundation for Cancer Research (AIRC) Investigator Grant, 29370 (PI Demichelis). 01/02/2024-01/01/2029. Non-invasive tracking of PARPi resistance clonal evolution in the plasma of prostate cancer patients. \$1,090,000 euros.

Prostate Cancer Foundation, US, 2024CHAL4434 (PIs Demichelis, Attard). 02/22/2025-02/21/2027. Temporal charting of treatment-related lethal prostate cancer lesions using liquid biopsies and multi-region tumor sequencing: development, testing, and validation of a computational framework within the PCF SELECT, PRIME, and PEACE consortia. \$450,000 USD to Demichelis.

Cancer Research UK-AIRC Accelerator Award Program, A26822/A22792 (PIs Demichelis, Attard). 11/01/2018-10/31/2025. Multi-modal clinical testing of prostate cancer patient plasma, PRIME. 5,700,000 euros.

Italian Ministry of University and Research, 2022Y9NP8K (PI Demichelis). 10/18/2023-10/17/2025. LIFT, Liquid biopsy and Functional imaging for hormone sensitive prostate cancer patients. \$188,729 euros.

Citations

1. Beltran H^{*&}, Romanel A^{*&}, Conteduca V, Casiraghi N, Sigouros M, Franceschini GM, Orlando F, Fedrizzi T, Ku S-Y, Dann E, Alonso A, Mosquera J-M, Sboner A, Xiang J, Elemento O, Nanus DM, Tagawa ST, Benelli M, **Demichelis F[&]**. (2020). Circulating tumor DNA profile recognizes transformation to castration resistant neuroendocrine prostate cancer. *J Clin Invest*, 130(4), 1653-1668. PMID: PMC7108892. Cited > 100.
2. Abida W, Cyrta J, Heller G, [... 30 authors ...], Scher HI, Kantoff P, Taplin M-E[#], Schultz N[#], De Bono JS[#], **Demichelis F[#]**, Nelson PS[#], Rubin MA[#], Chinnaiyan AM[#], Sawyers CL[#]. (2019). Genomic correlates of clinical outcome in advanced prostate cancer. *Proc Natl Acad Sci U S A*, 116(23), 11428-36. PMID: PMC6561293. Cited > 700.
3. Beltran H^{*&}, Prandi D^{*}, Mosquera JM, Benelli M, Puca L, Cyrta J, Marotz C, Giannopoulou E, Chakravarthi BV, Varambally S, Tomlins SA, Nanus DM, Tagawa ST, Van Allen EM, Elemento O, Sboner A, Garraway L[#], Rubin MA^{&#}, **Demichelis F^{&#}**. (2016). Divergent clonal evolution of androgen receptor indifferent castration resistant prostate cancer. *Nat Med*, 22(3), 298-305. PMID: PMC4777652. Cited > 1000.
4. Fracassi G, Lorenzin F[&], Orlando F, Gioia U, D'Amato G, Casaramona AS, Cantore T, Prandi D, Santer FR, Klocker H, d'Adda di Fagagna F, Mateo J, **Demichelis F[&]**. (2024). CRISPR/Cas9 screens identify LIG1 as a sensitizer of PARP inhibitors in castration-resistant prostate cancer. *J Clin Invest*, 135(4), e179393. PMID: PMC11827843

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2025	Organizing Committee member, Third JCA-AACR Precision Cancer Medicine International Conference, Kyoto, Japan, June 28-30, 2025
2024-present	Deputy Rector, University of Trento (UNITN), Italy
2024-present	Member designated by the Rector of the Academic Senate (UNITN), Italy
2024-present	Member, AACR Data Science Task Force
2024	Member, ESMO Congress 2025 Scientific Committee
2024	Education Committee Member, AACR Annual Meeting 2024
2023-present	Member, Scientific Standing Committee of the Pezcoller Foundation Symposia
2023	Guest Committee Member, Editorial Committee of the Annual Review of Cancer Biology
2023	Selection Committee member, 2023 Pezcoller Foundation-AACR International Award for Extraordinary Achievement in Cancer Research
2022-present	Vice-President of the Advisory Board of Hub Innovazione Trentino Foundation (HIT)
2022-2025	Vice-President of the Advisory Board of iNEST – Interconnected Nord-Est Innovation Ecosystem
2022-present	Member of the Vice-President for Research Board, European Consortium of Innovative Universities (ECIU) Alliance
2022-present	Member, Prostate Cancer UK - Scientific Advisory Board
2021-present	Vice-Rector, Research at UNITN, Italy
2021-present	Faculty member, Interdepartmental Center of Medical Sciences - CISMED, UNITN, Italy
2021, 2023,-	European Research Council, Deputy Panel Chair, Panel Member, ERC Advanced grants, LS4
2021, 2022	Reviewer Committee Member, German Cancer Aid, Translational Oncology Priority Program
2021	Review Panel Member, Collaborative research on tumor heterogeneity, clonal tumor evolution and therapy resistance, Federal Ministry of Education and Research, Germany
2021	Member, Swiss Cancer League, Review Board
2020	Remote Referee, "Excellent science" of H2020 Framework Programme, European Research Council Executive Agency (ERCEA)
2019-2022	Senior Editor, Molecular Cancer Research (MCR, AACR)
2018-present	Professor (BIO11), Department of Cellular, Computational and Integrative Biology, UNITN.
2018-present	Editorial Board member, European Urology Oncology
2017-2021	President, Transdisciplinary Program in Computational Biology Panel, International PhD Program in Biomolecular Sciences, UNITN
2016-2021	CIBIO Director's Delegate for Research SUA-RD, Health Science Programs, and UNITN Library
2015–2020	Scientific Fellowship Committee Member, Italian Association for Cancer Research Foundation
2014-2017	Associate Professor with tenure, Centre for Integrative Biology, UNITN
2013-present	Standing Member, Caryl and Israel Englander Institute for Precision Medicine at Weill Cornell Medicine and New York-Presbyterian Hospital, NY
2013-2019	Adjunct Assistant Professor, Computational Biomedicine, Institute for Computational Biomedicine, Weill Cornell Medicine, New York, NY

2011-2014 Assistant Professor, Computational Biology, Centre for Integrative Biology (CIBIO), UNITN
 2011-present Group Leader, Head of the Laboratory of Computational and Functional Oncology, UNITN
 2011-present Faculty member, International Ph.D. Program in Biomolecular Sciences, UNITN
 2011-2021 Member of the Executive Committee, International Ph.D. Program in Biomolecular Sciences
 2010-2018 Associate Editor, BMC Medical Genomics
 2010-2011 Faculty Member, Weill Cornell Graduate School of Medical Sciences, Program in Physiology, Biophysics, & Systems Biology, New York, NY
 2008-2011 Assistant Professor, Pathology and Laboratory Medicine, and Computational Biomedicine, Weill Cornell Medical College, New York, NY
 2008-2010 Member of Translational Research Committee, Weill Cornell Medicine, New York, NY
 2007-2008 Instructor, Pathology and Laboratory Medicine, and Institute Fellow at Institute for Computational Biomedicine, Weill Cornell Medical College, New York, NY
 2005-2010 Editorial Board member, Diagnostic Pathology
 2005-2007 Post-doctoral Fellow, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
 1997-2005 Research Associate, ITC-IRST (Fondazione Bruno Kessler) in Medical Informatics, Intelligent Data Analysis in Biomedicine, Automated Reasoning System Unit, Trento, Italy
 1996-1997 Scholarship at UNITN from the Istituto Nazionale Fisica della Materia (INFM). Title: Parallel computing for molecular dynamics simulations of monatomic glasses

Honors

2024 Premio "Armida Barelli" Università Cattolica Sacro Cuore Milano, Italy
 2021 Knight of the Order of Merit of the Italian Republic ("Cavaliere dell'Ordine 'Al merito della Repubblica Italiana") appointed by the President of the Italian Republic (n 16474 sVI, decr. 15/03/2021)
 2019-2023 "Highly Cited Researcher" by Clarivate Analytics and Web of Science
 2020 Premio Maria Teresa Messori Roncaglia ed Eugenio Mari ('ad uno Scienziato' 2020), Accademia Nazionale dei Lincei
 2018 Accelerator Award 2018 by CRUK-AIRC (with Attard, Basso, Caffo, De Giorgi, Tucci). PRIME for the use of liquid biopsy to accelerate clinical research
 2016 Prostate Cancer Foundation Challenge Award (with Beltran H, Attard G, Van Allen E, Chi K, Wyatt A, Rubin MA, Maher C). Development and Qualification of the PCF SELECT (Specific Evaluation in Liquid biopsies of Established prostate Cancer Targets) Plasma DNA Assay
 2014 Prostate Cancer Foundation Challenge Award (with Beltran H, Attard G). Early Detection of Neuroendocrine Prostate Cancer Transformation Using Circulating Genomic Signatures
 2011 Prostate Cancer Foundation Challenge Award. Proposal title: "Recurrent SPOP Mutations in Prostate Cancer: Characterization of a Potentially Targetable Sub-class of Prostate Cancer."
 2010 Department of Defense, USA, New Investigator Award. "Towards Understanding the Genetic Predisposition for Signalling Pathway Activation in Aggressive Prostate Cancer."
 2009 Dana-Farber Harvard Cancer Center SPORE Developmental Project Award. "Copy Number Variants Predisposing to ETS Rearrangements and Oncogenic Lesions."
 2008 Pilot Research Award for Translational and Cross-disciplinary Studies, Clinical and Translational Science Center at Weill Cornell Medical College, New York. "Towards the Identification of Germline Risk factors for Lethal Prostate Cancer."
 2008 STARR Cancer Consortium Award, Determining Germline Risk Factors for Lethal Prostate Cancer: The Role of Copy Number Variations in Prostate Cancer (#I2-A94- Co-recipient)
 2007 American Association for Cancer Research (AACR) Team Science Award, University of Michigan-Brigham and Women's Hospital Team
 2005 Prostate Cancer Foundation Competitive Awards, "Fusion of TMPRSS2 and ETS Family of Transcription Factors in Prostate Cancer."

C. Contributions to Science

1. **Digital Pathology and Machine Learning methods for *in situ* protein heterogeneity assessment.** Tissue Microarray platforms ensured the possibility to quantitatively and efficiently assess molecular and histomorphological features in the context of tumor diagnosis and prognosis. In the early days of Digital Pathology and high-throughput *in situ* assessment of tumor tissues, I developed pioneer approaches i. to remotely control robotized microscopes for intra-operative frozen section examination and ii. to digitalize histological

slides for the automated assessment of tissues while overcoming inter-observer variability. While optimizing the quantitative evaluation of immunohistochemistry slides, I observed that protein expression was often heterogeneous across tumor cells within the same tissue and hypothesized that this heterogeneity could serve as an independent predictor of patient outcome. This research led to multiple publications assessing prognostic/diagnostic biomarkers using hierarchical Naive Bayes models, including for ovarian, prostate, and hepatocellular carcinomas (Int J Cancer 2006, Neoplasia 2006 as co-first author; Cancer Res 2004).

- a. **Demichelis F**, Barbareschi M, Boi S, Clemente C, Dalla Palma P, Eccher C, Forti S. (2001). Robotic telepathology for intraoperative remote diagnosis using a still-imaging-based system. Am J Clin Pathol, 116(5), 744-52. PMID: 11710693
- b. **Demichelis F**, Barbareschi M, Dalla Palma P, Forti S. (2002). The virtual case: a new method to completely digitize cytological and histological slides. Virchows Arch, 441(2), 159-64. PMID: 12189506
- c. **Demichelis F**, Magni P, Piergiorgi P, Rubin MA, Bellazzi R. (2006). A hierarchical Naive Bayes Model for handling sample heterogeneity in classification problems: an application to tissue microarrays. BMC Bioinformatics, 7, 514. PMCID: PMC1698579
- d. **Demichelis F**, Sboner A, Barbareschi M, Dell'Anna R. (2006). TMABOOST: an integrated system for comprehensive management of tissue microarray data. IEEE Trans Inf Technol Biomed, 10(1), 19-27. PMID: 16445246

2. **Cancer genomics, tumor evolution studies, and germline-somatic synergies.** Upon the pivotal contributions to single base level definition of prostate cancer ETS rearrangement (Cancer Res 2006, Oncogene 2007, Cancer Res 2007, Genes Chromosomes Cancer 2009, Neoplasia 2010) and the complexity of prostate cancer primary disease (Nature 2010, Cell 2015, Cold Spring Harb Perspect Med, 2018), I co-led (with L. Garraway and MA Rubin) the first report on *Punctuated evolution* of prostate cancer genomes that first described Chromoplexy (Baca et al, Cell, 2013), by integrating inherited genetic signal and somatic event features - subsequently applied to other tumor types. Concomitantly, with a hypothesis-driven data-intensive methodology, my team demonstrated the interplay between germline variants and recurrent somatic aberrations that occur at tumor initiation, through *de novo* steroid biosynthesis.

- a. Prandi D, Baca SC, Romanel A, Barbieri CE, Mosquera J-M, Fontugne J, Beltran H, Sboner A, Garraway LA, Rubin MA, **Demichelis F**. (2014). Unraveling the clonal hierarchy of somatic genomic aberrations. Genome Biol, 15(8), 439. PMCID: PMC4167267
- b. Faltas BM*, Prandi D*, Tagawa ST, Molina AM, Nanus DM, Sternberg C, Rosenberg J, Mosquera J-M, Robinson B, Elemento O, Sboner A, Beltran H#, **Demichelis F**&#, Rubin MA&#. (2016). Clonal Evolution of Chemotherapy-resistant Urothelial Carcinoma. Nat Genet, 48(12),1490-1499. PMCID: PMC5549141
- c. Romanel A*, Garritano S*, Stringa B, Blattner M, Dalfovo D, Chakravarty D, Cotter KA, Petris G, Dhingra P, Gasperini P, Cereseto A, Elemento O, Sboner A, Khurana E, Inga A, Rubin MA, **Demichelis F**. (2017). Inherited determinants of early recurrent somatic mutations in prostate cancer. Nat Commun, 8(1), 48. PMCID: PMC5491529
- d. Gasperini P*, Alaimo A*, Stringa B*, Chung Y-M, Ciani Y, Lorenzin F, Fracassi G, Zekri Y, Orlando F, Quaini O, Gregoricchio S, Petris G, Casini A, Barbieri CE, Zwart W, Cereseto A, Sharifi N, Lunardi A#, **Demichelis F**#. (2025). Germline-somatic liaison dictates cancer subtype via de novo steroid biosynthesis. Cancer Discov. Online ahead of print. PMID: 40512155

3. **Molecular features of AR-negative prostate cancer evidence a pivotal role of epigenetic reprogramming as part of lineage plasticity.** Resistance mechanisms in prostate cancer are diverse, dependent on the biological pathways targeted, and typically occur in the context of activated androgen receptor (AR) signaling. While AR is the main key driver of prostate cancer initiation and progression, a subset of prostate cancers either start relatively AR-independent or, more commonly, acquire AR-independence during the course of their disease. The Demichelis laboratory significantly contributed to the definition of the molecular determinants of AR-independent prostate cancer across genomics, transcriptomics, and epigenetics and treatment resistance mechanisms. This interdisciplinary work was conducted in collaboration with multiple institutions, including Weill Cornell Medicine, the DFCI, Memorial Sloan Kettering (Mu et al, Science, 2017), and the University of Bern (Cyrta et al, Nat Commun, 2020).

a.b.c. See CITATIONS 1., 2., and 3.

- d. Franceschini GM, Quaini O, Mizuno K, [...], Haffner MC, Attard G, Aparicio A, **Demichelis F**&#, Beltran H&#. (2024). Non-invasive detection of neuroendocrine prostate cancer through targeted cell-free DNA methylation. Cancer Discov, 14(3), 424-445. PMCID: PMC10905672

4. **Methodological and analytical approaches to extract clinically relevant features from next-generation sequencing data of human tumors to nominate tumor evolution paths and synthetic lethal candidates.** Driven by open clinical questions in the setting of human tumors, the Demichelis laboratory developed computational and analytical tools over the years to model heterogeneity, fingerprint human DNA, infer individual ethnicity to properly stratify patients, quantify tumor cellularity, chart evolution, quantify the genomic backbone of tumors at allele-specific level, nominate synthetic lethal partners through integrative analysis of genomic and transcriptomic, and study tumor type-specific differential methylation, while engaging cutting edge technologies.
 - a. Ciani Y*, Fedrizzi T*, Prandi D*, Lorenzin F, Locallo A, Gasperini P, Franceschini GM, Benelli M, Elemento O, Fava LL, Inga A, **Demichelis F.** (2022). Allele-specific genomic data elucidates the role of somatic gain and copy number neutral loss of heterozygosity in cancer. *Cell Syst*, 13(2), 183-193.e7. PMCID: PMC8856743
 - b. Fedrizzi T*, Ciani Y*, Lorenzin F, Cantore T, Gasperini P, **Demichelis F.** (2021). Fast Mutual Exclusivity algorithm nominates potential synthetic lethal gene pairs through brute force matrix product computations. *Comput Struct Biotechnol J*, 19, 4394-4403. PMCID: PMC8369001
 - c. Benelli M*, Franceschini GM*, Magi A, Romagnoli D, Biagioni C, Migliaccio I, Malorni L, Di Leo A, **Demichelis F.** (2021). Charting differentially methylated regions in cancer with Rocker-meth. *Commun Biol*, 4(1), 1249. PMCID: PMC8563962
 - d. Cantore T, Gasperini P, Bevilacqua R, Ciani Y, Sinha S, Ruppini E, **Demichelis F.** (2025). PRODE recovers essential and context-essential genes through neighborhood-informed scores. *Genome Biol*, 26(1), 42. PMCID: PMC11869679
5. **Nucleic acids circulating in the blood of prostate cancer patients trace tumor dynamics and require dedicated solutions, especially in the context of low tumor fractions.** Liquid biopsies are a master source of tumor information to be exploited for biomarkers of diagnosis, prognosis, and treatment response. Tumor type-specific genomic features call for tailored solutions for appropriate detection sensitivity at low and moderate circulating tumor DNA (ctDNA) fractions. The Demichelis laboratory hypothesized that *ad hoc* cfDNA solutions would overcome challenging features of metastatic prostate cancer, characterized by structural changes, heterogeneity, and aneuploidy, and, as part of an international collaboration, led the development of the PCF_SELECT assay to be used in a range of clinical trial cohorts. Building on collaborative work on the characterization and isolation of extracellular vesicles (J Extracell Vesicles 2018, RNA Biol 2017; EBioMedicine, 2019; Cell Rep Med. 2025), the laboratory developed procedures to optimize the concomitant isolation of multiple analytes from single plasma aliquots (ONCE approach; Mugoni et al, J Extracell Biol, 2023), including vesicle RNAs (Mugoni et al, Cancer Letters, 2022), and to integrate EV genomic and transcriptomic features (chair of the ISEV workshop *QuantitatEVs: from bulk to single EV analysis*, Jan-Feb 2023, Trento). The liquid biopsy work has been developed within an international multi-institutional program to develop advanced prostate cancer assays with the University College of London and five Italian clinical centers (Demichelis PI, Attard co-PI).
 - a. Orlando F, Romanel A, Trujillo B, Sigouros M, Wetterskog D, Quaini O, Leone G, Xiang JZ, Wingate A, Tagawa S, Jayaram A, Linch M, PEACE# consortium, Jamal-Hanjani M, Swanton C, Rubin MA, Wyatt AW, Beltran H, Attard G#, **Demichelis F#.** (2022). Allele-informed copy number evaluation of plasma DNA samples from metastatic prostate cancer patients: the PCF_SELECT consortium assay. *NAR Cancer*, 4(2), zcac016. PMCID: PMC9154344
 - b. Mugoni V, Ciani Y, Quaini O, Tomasini S, Notarangelo M, Vannuccini F, Marinelli A, Leonardi E, Pontalti S, Martinelli A, Rossetto D, Pesce I, Mansy SS, Barbareschi M, Ferro A, Caffo O, Attard G, Di Vizio D, D'Agostino VG#, Nardella C#, **Demichelis F#.** (2023). Integrating extracellular vesicle and circulating cell-free DNA analysis using a single plasma aliquot improves the detection of HER2 positivity in breast cancer patients. *J Extracell Biol*, 2(9), e108. PMCID: PMC10688391
 - c. see 3.d
 - d. Leone G, Orlando F, [...], James ND, **Demichelis F#**, Attard G#. (2025). Plasma DNA androgen receptor alterations after intensified hormonal treatment for advanced prostate cancer in the STAMPEDE trial. *JAMA Oncol*. 2025 Feb 27. PMID: 40014335

Publication metrics (Scopus at 2025.07.08): h-index=70, citations>33,000.