

BIOGRAPHICAL SKETCH

NAME: Demichelis, Francesca

eRA COMMONS USER NAME (credential, e.g., agency login): demichelis123

POSITION TITLE: Professor, University of Trento

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Trento, Trento, I	MS	10/1996	Physics
University of Trento, Trento, I	PhD	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 over 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 that then 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, including 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 liquid biopsy 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:

The NIH R01CA287075-01A1, MPI (DI VIZIO contact, STOTT, DEMICHELIS). 2024/09/01- 2029/08/31. Clinical Translation of a Large Oncosome-Based Prostate Cancer Blood Test (PLUS).

The 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.

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.

Cancer Research UK-AIRC Accelerator Award Program, A26822/A22792 (PI Demichelis). 11/01/18-10/31/25. Multi-modal clinical testing of prostate cancer patient plasma, PRIME.

NCI P50 CA211024-01A1, Prostate Cancer SPORE, Project 1 (Co-PI Beltran, Demichelis). 01/01/18-07/31/22. Non-Invasive Clinical Assay for Early Detection of Treatment Resistance in Patients with Metastatic Prostate Cancer.

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**[&]. Circulating tumor DNA profile recognizes transformation to castration resistant neuroendocrine prostate cancer. *J Clin Invest*. 2020 Feb 24. 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[#]. Genomic correlates of clinical outcome in advanced prostate cancer. *Proc Natl Acad Sci U S A*. 2019 Jun 4;116(23):11428-11436. PMID: PMC6561293. Cited > 700.
 3. Romanel A*, Gasi Tandefelt D*, Conteduca V, Jayaram A, Casiraghi N, Wetterskog D, Salvi S, Amadori D, Zafeiriou Z, Rescigno P, Bianchini D, Gurioli G, Casadio V, Carreira S, Goodall J, Wingate A, Ferraldeschi R, Tunariu N, Flohr P, De Giorgi U, de Bono JS, **Demichelis F**^{&#}, Attard G^{&#}. Plasma AR and Abiraterone Resistant Prostate Cancer. *Sci Transl Med*. 2015 Nov 4;7(312):312re10. PMID: PMC6112410. Cited > 340.
 4. 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**^{&#}. Divergent clonal evolution of androgen receptor indifferent castration resistant prostate cancer. *Nat Med*. 2016 Mar;22(3):298-305. PMID: PMC4777652. Cited > 1000.

B. Positions, Scientific Appointments and Honors

Positions

- 2024-present Vice-Rector of the University of Trento (UNITN), Italy;
- 2024-present Member designated by the Rector of the Academic Senate (UNITN), Italy;
- 2022-present Vice-President of the Advisory Board of Hub Innovazione Trentino Foundation (HIT);
- 2022-present Vice-President of the Advisory Board of iNEST – Interconnected Nord-Est Innovation Ecosystem
- 2022-present European Consortium of Innovative Universities (ECIU) Alliance, Member of the Vice-President for Research Board;
- 2021-present Vice-Rector for Research at UNITN, Italy;
- 2018-present Professor (BIO11), Department of Cellular, Computational and Integrative Biology, UNITN.
- 2014-2017 Associate Professor with tenure, Centre for Integrative Biology, UNITN.
- 2011-2014 Assistant Professor in Computational Biology, Centre for Integrative Biology (CIBIO), UNITN.
- 2011-present Group Leader, Head of the Laboratory of Computational and Functional Oncology, UNITN.
- 2008-2011 Assistant Professor in Pathology and Laboratory Medicine, and in Computational Biomedicine, Weill Cornell Medical College, New York, NY.
- 2007-2008 Instructor in Pathology and Laboratory Medicine, and Institute Fellow at Institute for Computational Biomedicine, Weill Cornell Medical College, New York, NY.
- 2005-2007 Post-doctoral Fellow at the Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.
- 1997-2005 Research Associate at 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.

Scientific Appointments

- 2023-present Scientific Standing Committee of the Pezcoller Foundation Symposia member;
- 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 Prostate Cancer UK - Scientific Advisory Board member;
- 2021-present Faculty member at Interdepartmental Center of Medical Sciences - CISMED, UNITN, Italy;
- 2021,2022 German Cancer Aid, Reviewer Committee Member for Translational Oncology Priority Program;
- 2021 Federal Ministry of Education and Research, Germany, Review Panel Member "Collaborative research on tumor heterogeneity, clonal tumor evolution and therapy resistance".
- 2021 Swiss Cancer League, Review Board Member;
- 2021 European Research Council, Deputy Panel Chair, Panel Member, ERC Advanced grants, LS4;
- 2020 European Research Council Executive Agency (ERCEA), Remote Referee for "Excellent science" of H2020 Framework Programme;
- 2019-2022 Senior Editor, Molecular Cancer Research (MCR, AACR);
- 2018-present Editorial Board member, European Urology Oncology;

2017-2021 President of the 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 Italian Association for Cancer Research Foundation, Scientific Fellowship Committee Member;
 2013-present Standing Member of the Caryl and Israel Englander Institute for Precision Medicine at Weill Cornell Medicine and NewYork-Presbyterian Hospital, NY;
 2013-2019 Adjunct Assistant Professor of Computational Biomedicine in the Institute for Computational Biomedicine, Weill Cornell Medicine, New York, NY
 2011-present Faculty member of the International Ph.D. Program in Biomolecular Sciences, UNITN;
 2011-2021 Member of the Executive Committee of International Ph.D. Program in Biomolecular Sciences;
 2010-2018 Associate Editor, BMC Medical Genomics;
 2010-2011 Faculty Member of Weill Cornell Graduate School of Medical Sciences, Program in Physiology, Biophysics, & Systems Biology, New York, NY;
 2008-2010 Member of Translational Research Committee, Weill Cornell Medicine, New York, NY;
 2005-2010 Editorial Board member, Diagnostic Pathology;

Honors

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*" in 2019/2020/2021/2022/2023 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, M.A., 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. Robotic telepathology for intraoperative remote diagnosis using a still-imaging-based system. Am J Clin Pathol 2001;116:744-52.
- b. **Demichelis F**, Barbareschi M, Dalla Palma P, Forti S. The virtual case: a new method to completely digitize cytological and histological slides. Virchows Arch 2002;441:159-64.
- c. **Demichelis F**, Magni P, Piergiorgi P, Rubin MA, Bellazzi R. A hierarchical Naive Bayes Model for handling sample heterogeneity in classification problems: an application to tissue microarrays. BMC Bioinformatics 2006;7:514.
- d. **Demichelis F**, Sboner A, Barbareschi M, Dell'Anna R. TMABOOST: an integrated system for comprehensive management of tissue microarray data. IEEE Trans Inf Technol Biomed 2006;10:19-27.

2. Prostate cancer genomics and tumor evolution studies. Understanding the genomic landscape of primary and metastatic prostate cancer was accelerated by the advent of high-density arrays and next-generation sequencing platforms. Upon the pivotal contributions to the definition of prostate cancer ETS rearrangement breakpoints at the single base level (Cancer Res 2006, Oncogene 2007, Cancer Res 2007, Genes Chromosomes Cancer 2009, Neoplasia 2010) and of the complexity of primary disease (Nature 2010, Cell 2015, Cold Spring Harb Perspect Med. 2018), I focused on the characterization of prostate cancer molecular determinants of aggressive disease by combining inherited and somatic features (PNAS 2012, Cancer Epidemiol Biomarkers Prev 2010). I co-led the first report on *Punctuated evolution* of prostate cancer genomes that first described Chromoplexy, a complex genomic catastrophic event, and, based on the etiology of prostate cancer, I hypothesized an interplay between germline variants and specific recurrent somatic aberrations (as SPOPmt and ERG rearrangement) that occurs at tumor initiation. These studies resulted in the development of computational approaches to charting tumor evolution, applied to GU cancers (funded by ERC-CoG, 648670).

- a. Baca SC, Prandi D, Lawrence MS, Mosquera J-M, [... 23 authors ...], Voet D, Ramos AH, Winckler W, Cipicchio M, Ardlie K, Kantoff PW, Berger MF, Gabriel SB, Golub TR, Meyerson M, Lander ES, Elemento O, Getz G, **Demichelis F**[#], Rubin MA[#], Garraway LA[#]. Punctuated Evolution of Prostate Cancer Genomes. Cell. 2013 Apr 25;153(3):666-77.
- b. 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**. Inherited determinants of early recurrent somatic mutations in prostate cancer. Nat Commun. 2017 Jun 29;8(1):48.
- c. Prandi D., Baca S.C., Romanel A., Barbieri C.E., Mosquera J-M., Fontugne J., Beltran H., Sboner A., Garraway L.A., Rubin M.A., **Demichelis F**. Unraveling the clonal hierarchy of somatic genomic aberrations. Genome Biol. 2014 Aug 26;15(8):439.
- d. 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[#]. Clonal Evolution of Chemotherapy-resistant Urothelial Carcinoma. Nat Genet. 2016 Dec;48(12):1490-1499.

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 4.

- d. Franceschini GM, Quaini O, Mizuno K, [...], Haffner MC, Attard G, Aparicio A, **Demichelis F**[#], Beltran H[#]. Non-invasive detection of neuroendocrine prostate cancer through targeted cell-free DNA methylation. Cancer Discov. 2024 Jan 10. doi: 10.1158/2159-8290.CD-23-0754. PMID: 38197680

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**. Allele-specific genomic data elucidates the role of somatic gain and copy number neutral loss of heterozygosity in cancer. *Cell Syst*. 2022 Feb 16;13(2):183-193.e7.

b. Fedrizzi T*, Ciani Y*, Lorenzin F, Cantore T, Gasperini P, **Demichelis F**. Fast Mutual Exclusivity algorithm nominates potential synthetic lethal gene pairs through brute force matrix product computations. *Comput Struct Biotechnol J*. 2021 Aug 5;19:4394-4403.

c. Benelli M*, Franceschini GM*, Magi A, Romagnoli D, Biagioni C, Migliaccio I, Malorni L, Di Leo A, **Demichelis F**. Charting differentially methylated regions in cancer with Rocker-meth. *Commun Biol*. 2021 Nov 2;4(1):1249.

d. Benelli M, Romagnoli D, **Demichelis F**. Tumor purity quantification by clonal DNA methylation signatures. *Bioinformatics*. 2018 Jan 8. doi: 10.1093/bioinformatics/bty011.

5. Nucleic acids circulating in the blood of prostate cancer patients trace tumor dynamics and require dedicated solutions 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 trials cohorts. Through collaborative work with Dr. Di Vizio, the laboratory contributed to the molecular characterization of circulating large oncosomes (LO) (J Extracell Vesicles. 2018, RNA Biol. 2017) and to the characterization of a charged-based method for the isolation of extracellular vesicles (Notarangelo et al., EBioMedicine. 2019). The laboratory is investing in tuning 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 (see the ISEV workshop, titled *QuantitatEVs: from bulk to single EV analysis*, Jan-Feb 2023, Trento). I lead an international multi-institutional program to develop cfDNA assays for advanced prostate cancer with the University College of London, and five Italian clinical centers.

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#**. Allele-informed copy number evaluation of plasma DNA samples from metastatic prostate cancer patients: the PCF_SELECT consortium assay. *NAR Cancer*. 2022 May 27;4(2):zcac016.

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#**. 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*. Volume 2, Issue 9 September 2023 e108. doi/10.1002/jex2.108.

c. see 3.d

d. Basso M, Gori A, Nardella C, [...], Witwer KW, Bussolati B, Di Vizio D, Falcon Perez J, Lenassi M, Cretich M, **Demichelis F**. ISEV Workshop. International Society for Extracellular Vesicles Workshop. QuantitatEVs: multiscale analyses, from bulk to single extracellular vesicle. *J Extracell Biol*. 2024 Jan;3(1):e137. doi: 10.1002/jex2.137. Epub 2024 Jan 24.

Publication metrics (Scopus at 20241218): h-index=68, citations>31,000.