

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: Scorletti, Eleonora

Persistent Identifier (PID) of the Senior/Key Person: <https://orcid.org/0000-0002-7547-146X>

Position Title: Assistant Professor

Organization and Location: Johns Hopkins University , Baltimore, Maryland, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
University of Pennsylvania, Philadelphia, PA, Philadelphia, Pennsylvania, United States	Postdoctoral Fellow	09/2018	08/2023	MASLD and liver metabolism
University of Southampton, Southampton , Not Applicable, N/A, United Kingdom	Doctor of Philosophy (PHD)	10/2014	10/2018	MASLD and liver metabolism
University Hospital Southampton, UK, Southampton , Not Applicable, N/A, United Kingdom	Fellow	01/2011	07/2018	Diabetes, Obesity and Metabolism
University of Pavia, Pavia, Not Applicable, N/A, Italy	Resident	07/2007	07/2011	Preventive Medicine Diabetes and Obesity
University of Pavia, Pavia, Not Applicable, N/A, Italy	Fellow	11/2005	06/2007	Diabetes and Obesity
University of Pavia, Pavia, Not Applicable, N/A, Italy	Doctor of Medicine (MD)	09/1999	10/2005	Medicine

Appointments and Positions

2026 - present Assistant Professor, Johns Hopkins University , Baltimore, Maryland, United States
 2023 - 2026 Instructor of Genetics, University of Pennsylvania, Philadelphia, PA, Philadelphia, Pennsylvania, United States

Certification:

I certify that the information provided is current, accurate, and complete. This includes, but is not limited to, information related to current, pending, and other support (both foreign and domestic) as defined in 42 U.S.C. § 6605.

In accordance with Section 10632 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19232), each individual identified as a senior/key person must certify that they are not a party to a malign foreign talent recruitment program.

Research Security Training Requirement for Federal Award Personnel: In accordance with Section 10634 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19234), each individual identified as a senior/key person must certify that they have completed the requisite research security training that meets the requirements specified in Item 2 of Important Notice No. 149 within 12 months prior to proposal submission.

Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§287, 1001, 1031 and 31 U.S.C. §§3729-3733 and 3802.

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NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: Scorletti, Eleonora

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Position Title: Assistant Professor

Organization and Location: Johns Hopkins University , Baltimore, Maryland, United States

Personal Statement

I am a translational physician-scientist with specialized training in Preventive Medicine. My research centers on the regulation of lipid metabolism in metabolic diseases and aging, and I focus particularly in the heterogeneity of steatotic liver disease. I employ a recall-by-genotype, deep-phenotyping strategy in humans as a model system, allowing me to investigate how specific genetic variants impact disease mechanisms, clinical presentation, and therapeutic response in metabolic disorders. During my doctoral training at the University of Southampton (UK), under the mentorship of Dr Christopher Byrne and Dr Philip Calder, I investigated both the effects of omega-3 fatty acid treatment on NAFLD and the effects of synbiotics (*Bifidobacterium animalis* subsp. *lactis* BB-12 plus fructo-oligosaccharide) on meta-organismal pathways responsible for dyslipidemia, intestinal permeability, nutrient absorption, gut hormones production, metabolic inflammation and NAFLD. My work led to several first- author publications demonstrating that DHA+EPA treatment drives tissue DHA enrichment and reduces liver fat percentage (Scorletti et al., *Hepatology* 2014) and that the PNPLA3-I148M is associated with a decreased response to DHA+EPA treatment (Scorletti et al., *J Hepatology* 2015). Moreover, my work on gut microbiota and NAFLD demonstrated that synbiotics treatment alter fecal microbiomes, but not liver fat or fibrosis (Scorletti et al., *Gastroenterology* 2020). For my postdoctoral training, I joined the laboratory of Dr Rotonya Carr at the University of Pennsylvania (USA). Building on my previous research, I started investigating the effects of a recently discovered Perilipin 2 missense polymorphism PLIN2-Pro251 on hepatocellular lipid droplet biology (funded by the AASLD awarded me the Afdhal/ Mchutchison Lifer Award). In 2021, after Dr Carr accepted a position at the University of Washington, I joined Dr Daniel Rader's laboratory. Here, I continued my work on PLIN2-Pro251 but also broadened my research to explore the impact of vitamin E intake in patients with NAFLD, leading to two first-authored publication (Scorletti et al., *JHEP. Reports* 2023; Scorletti et al., *Am. J. Gastroenterol.* 2022). In 2023, I was awarded the highly competitive, peer- reviewed Penn Junior Investigator Pilot Grant Program (JIPGP), enabling me to commence recall-by-genotype to deep phenotype PNPLA3-I148M homozygous carriers. Most recently, I was awarded the NIH/NIDDK K99 Pathway to Independence Award. Since my research focuses on metabolic diseases, I am investigating how PNPLA3 I148M and other genetic variants interact with aging to influence adipose tissue eicosanoid production. This research project is supported by an NIH-NIA R21 (1st percentile). In parallel, supported by the University of Pennsylvania Diabetes Research Center Pilot and Feasibility Grant, I am investigating GLP1R genetic variants that impact GLP1R agonist efficacy. Moving forward, my research will expand by characterizing additional genetic variants (including HSD17B13, TM6SF2, MBOAT7, and CIDEA) that influence lipid droplet metabolism. Beyond liver disease, I will extend these approaches to other metabolic conditions, including type 2 diabetes and obesity, with a focus on genetic determinants of treatment response. This underscores my commitment to applying human-based approaches to elucidate the genetic drivers of metabolic disease and aging.

Honors

2024	Edward Holmes Clinical Research Award for Early Career Faculty Department of Medicine Research Day, Perelman School of Medicine, University of Pennsylvania
2024 - 2026	K99/Pathway to Independence Award, NIH/NIDDK
2023	Abstract Award: Penn Obesity Symposium, University of Pennsylvania
2020 - 2022	Two years fellowship: AASLD AFDHAL/MCHUTCHISON L.I.F.E.R. AWARD, American Association for the Study of Liver Disease
2017 - 2018	Clinical Research Fellowship in nutrition and metabolism awarded by Parnell Diabetes Trust at the Southampton NIHR Biomedical Research Centre, University of Southampton
2011	Research Fellowship award to conduct research at the Southampton NIHR Biomedical Research Centre, University of Pavia, Italy
2008	Research project funding award (Hôpital Général d'Ayamé, Cote D'Ivoire), Cariplo Foundation Bank (Italy)

Contributions to Science

1. Omega-3 fatty acids treatment on NAFLD I investigated the effect of omega-3 fatty acid treatment in patients with NAFLD. I was the first author of the publications that analyzed the primary and secondary outcomes of the WELCOME study (NCT00760513), showing that DHA+EPA treatment successfully reduces liver fat percentage in NAFLD patients. These papers have had a profound impact on public health policy in the United Kingdom, as the data and recommendations expressed therein were relied upon by the United Kingdom-National Institute for Clinical Excellence (NICE) when it reformulated its guidelines for omega-3 fatty acid treatment in NAFLD (NAFLD: Assessment and Management, NICE Guideline NG49, July 2016). In effect, my work directly informed therapeutic approaches for NAFLD patients in the UK (13 million people).
2. PNPLA3-I148M and PLIN2-Ser251Pro gene variants and NAFLD. I have investigated the association between PNPLA3-I148M and an increased risk of NAFLD progression and severity from several angles. First, I have studied the associations between NASH and BMD values, and between PNPLA3 I148M genotypes and BMD, in adolescents with NAFLD. This research showed that, taken together, the independent associations between: (a) low BMD and PNPLA3 CG+GG genotype; (b) low BMD and NASH; and (c) PNPLA3 CG+GG genotype and NASH, provide support for a causal relationship between NASH and low BMD. Second, I showed that among patients with NAFLD, PNPLA3-I148M carriers have a decreased response to DHA+EPA treatment. Currently, I have investigated whether a variant in the gene responsible for the production of PLIN2 (Ser251Pro) protein affects liver lipid accumulation and NAFLD. To this end, I have investigated whether PLIN2-Pro251 plays a role in the progression of NAFLD/NASH in a in vivo model, by generating hepatocytespecific PLIN2-Pro251 mice and feeding them a diet high in fructose, fat, and cholesterol which has been shown to produce steatosis, inflammation, and fibrosis. In parallel, I have analyzed two large cohorts of patients - the Million Veteran Program (MVP) and the Penn Medicine Biobank (PMBB) - using a candidate gene approach to identify the clinical and metabolic traits of patients with PLIN2-Pro251 risk alleles. My results provide insights into the role of PLIN2-Pro251 in NAFLD and offer information potentially relevant to the development of therapeutic strategies aimed at inhibiting the accumulation of lipid droplets in the liver.
3. Gut microbiota dysbiosis and NAFLD. In the INSYTE study (NCT01680640), I investigated the effects of synbiotic (subsp. lactis BB-12 plus fructooligosaccharide) treatments in patients with NAFLD. I showed that synbiotic treatment is effective in changing gut microbiota, but this pro- and prebiotic combination is ineffective in improving liver fat content or liver fibrosis markers. My first authored paper examining the results obtained from this study has affected the views on the use of synbiotic as a treatment for NAFLD. Specifically, my findings have been cited in the Cochrane Review dealing with NAFLD (Nutritional supplementation for nonalcohol-related fatty liver disease: a network meta-analysis).
4. Nutrition and NAFLD (Vitamin E and Alcohol). I have studied dietary vitamin E intake with disease phenotypes and evaluated the association between vitamin E levels and the development of NAFLD. Using Data from >210,000 participants, I showed that increased dietary vitamin E is associated with reduced rates of several gastrointestinal diseases as well as overall mortality and that diabetic and overweight subjects with increased vitamin E intake have fewer NAFLD diagnoses. These findings suggest that further mechanistic and therapeutic investigations are warranted to better understand the relevance of vitamin E consumption for gastrointestinal diseases. In addition, I have studied the effects of alcohol on hepatic lipid metabolism, body composition, energy homeostasis, and insulin sensitivity as measured by hyperinsulinemic-euglycemic clamp. Our results demonstrated that hepatic ceramide reduction ameliorates the effects of alcohol on hepatic lipid droplet (LD) accumulation by promoting VLDL secretion and lipophagy, the latter of which involves ceramide cross-talk between the lysosomal and LD compartments. We additionally demonstrate that hepatic ceramide reduction prevents alcohol's inhibition of hepatic insulin signaling. These effects on the liver are associated with a reduction in oxidative stress markers and are relevant to humans, as we observe peri-LD ASAH expression in human ALD. Together, our results suggest a potential role for hepatic ceramide inhibition in preventing ALD.
5. Methodologies to diagnose and monitor NAFLD. We analyzed the different investigations currently available to diagnose and monitor NAFLD, highlighting the variation in international guidelines (European, US and NICE), particularly regarding the use of liver ultrasonography. Treatment options are beyond the scope of this article. Based on these data, we suggested ultrasound scan as first line investigation for subjects with increased ALT and LFT levels. This research was subsequently included in the United Kingdom-National Institute for Clinical Excellence (NICE) guidelines for the diagnosing and monitoring of non-alcoholic fatty liver disease in adults.

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