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Epigenetics and Policy: cross-linking the 'environmental turn' in the life sciences and the 'molecular turn' in epidemiology

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ABSTRACT

This thesis is an empirical investigation of epigenetics and policy. This research first focused on mapping the impact of epigenetics in health care and exploring the challenges it poses for health care policy. The thesis developes a combined qualitative-quantitative strategy to identify the most active areas of epigenetic research, clinical applications and clinical outputs, as well as to track the number of publications on epigenetics. Moreover, the thesis finds that the science of epigenomics goes 'beyond the genome' insofar as what lies beyond can be conceptualised through and converted into genome-friendly, code-compatible digital representations. The research further focused on the case of Glasgow, a city characterized by stark health and social inequalities, where epigenetics has been employed in an interdisciplinary project to measure and instruct relevant social programs to target these inequalities. This thesis thus contributes a critical insight into how epigenetics is currently employed – in collaboration between actors of diverse backgrounds; and in policy efforts and action upon health. The thesis finds that within this project epigenetics is conceptualised as instrumentally effective, policy-approprate evidentiary resource that could foster socio-political change in a non-distant future. Accordingly, it is thanks to its molecularization of the environment and therefore its purported objectivity, that epigenetics is bestowed the potential for actionable public health knowledge. Additionally, the thesis finds that it is the solidary practice that governs this interdisciplinary collaborative endeavour in Glasgow.

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LIST OF ABBREVIATIONS

5mC – 5-methylcytosine

5hmC – 5-hydroxymethylcytosine

AIDs – Autoimmune Diseases

ALSPAC – Avon Longitudinal Study of Parents and Children

BMJ – British Medical Journal

CpG – Cytosine-Guanine dinucleaptides

CVDs – Cardiovascular Diseases

DG-RTD – European Commission Directorate General for Research

DNMT – DNA methyltranferase

DNMTi – DNA methyltransferase inhibitor

ELSI – Ethical, Legal and Social Implications of science

EJHG – European Journal of Human Genetics

EMA – European Medicines Agency

EPIC – European Prospective Investigation into Cancer and Nutrition

EPIGEN – Italian Epigenetics Consortium

EpiStressNet – Epigenetics and Stress Network

EU – European Union

EU-CTR – European Union Clinical Trial Register

FC – Football Club

GCPH – Glasgow Centre for Population Health

FDA – United States Food and Drug Administration

HDAC – Histone Deacetylation

HDACi – Histone Deacetylation inhibitor

IHEC – International Human Epigenome Consortium

IJE – International Journal of Epidmiology

iPSCs – induced Pluripotent Stem Cells

NCI – National Cancer Institute

NIH – National Insitute of Health

NHS – National Health Services

NDDs – Neurodegenerative diseases

pSoBid – Psychological, social and biological determinants of ill health cohort

PTM – Post-Translational Modifiations of proteins

STS – Science and Technology Studies

T2D – Type 2 diabetes mellitus

US – United States

UK – United Kingdom

WHO – World Health Organisation

WHO/Europe – World Health Organisation Regional Office for Europe

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CHAPTER ONE - INTRODUCTION

This thesis is an empirical investigation of epigenetics and policy. This research first focused on mapping the impact of epigenetics in health care and exploring the challenges it poses for health care policy. The research further focused on a particular project in Glasgow, in which epigenetics was employed in research with the aim to foster political action upon health called the psychological, social and biological determinants of ill health (pSoBid) project. Drawing on the empirical data on Glasgow case, the thesis finds that epigenetics represents an instrumentally effective, policy-apprpriate evidentiary resource, that could foster socio-political change by virtue of its purported 'objectivity', conferred by its 'molecularization of the environment, biography and milieu (Landecker 2011; Niewöhner 2011). Additionally, the thesis finds that the research and action upon health in Glasgow is governed by communal solidarity, i.e. solidary practice (Prainsack and Buyx 2012).

INTRODUCTION

Epigenetics is an emerging science that studies changes in gene expression that do not involve changes to the underlying DNA sequence. Ever since the completion of the reference sequence of the human genome, most efforts of the scientific community have been directed to understanding how the linear nucleotide sequence of DNA is employed in cellular activities in development and pathological conditions. In the words of the Italian Epigenetics Consortium:

> "Upon completion of the Human Genome Project in 2003, it became evident that the information for life is encoded not only in the DNA sequence but also in the chemical modifications deposited by enzymes both on DNA and its associated Histone proteins. These are known as "epigenetic modifications", which alter gene expression while the DNA sequence remains unchanged." (The Italian Epigenetics Consortium, EPIGEN)

Much of today's epigenetic science means studying the multiple modifications to which DNA or histone proteins are subjected, and consequently how such modifications affect overall nucleosome and chromatin structure (Goldberg et al. 2007). The overwhelming technological development in recent years made it possible to assay such modifications at the level of a *single* gene or modification, as well as to describe them across the *whole genome* (Callinan and Feinberg 2006). A *genome-wide* set of modifications made to DNA and the protein scaffold that supports it is called the 'epigenome' and the science that studies it 'epigenomics'. Epigenomics science thus consists of a "global, comprehensive view of sequence-independent processes that modulate gene expression patterns in a cell" (Rivera and Ren 2013, 39).

In the last couple of years, many national and supranational epigenomic projects and/or consortia were initiated. These projects aim to generate freely available, high-resolution reference maps of epigenomes 'for normal and disease cell types' in both humans and animal models. The Human International Epigenome

Consortium (IHEC[1]) states that these epigenome reference maps 'are likely to have an immediate impact on the understanding of many diseases, and will hopefully lead to the discovery of new means to treat and manage them'. Among the diseases that have been linked to epigenetic aberrations are cancer (Esteller 2007; Kulis and Esteller 2010; Sandoval and Esteller 2012), neurodegenerative (Urdinguio et al. 2009) and autoimmune diseases (Brooks et al 2010), as well as cardiovascular (Ordovàs and Smith 2010) and metabolic diseases (Schwenk, Vogel and Schuermann 2013), etc.

The World Health Organisation (WHO) marked these diseases as the major contributors to the burden of disease in both 'developed' and 'developing' countries (WHO 2012). The WHO links the development of these diseases with 'life style factors' such as smoking, physical activity and diet, and alcohol intake, as well as with 'social factors' like poverty (WHO 2015). The associations between epigenetic changes and environmental factors such as socio-economic status (McGuinness et al 2012), smoking (Shenker et al 2013), air pollution (Baccarelli et al 2009), nutrition (Heijmans et al 2008), etc. have indeed already been reported in cohort studies. Speculations over epidemiological research suggest that the effects of diet or smoking are transmitted into next generations in virtue of yet unknown epigenetic mechanism (Pembrey 2006). Findings in animal studies suggest that some epigenetic changes can travel across generations (e.g. Padmanabhan *et al*. 2013; Lambrot *et al*. 2013; Dias and Ressler 2014). However, this idea is highly disputed in the scientific community and especially controversial when extended to humans.

[1] Available at: http://ihec-epigenomes.org (Last accessed on 12.12.2016)
[2] Available at http://www.deutsches-epigenom-programm.de/epigenomics/ (Last accessed on

Epigenetics research outputs have already made it into the clinic and many are expected to do so in the near future. Investigations of epigenetics are contributing to normative debates on responsibility for health (Wiener 2010, Hedlund 2011, Chadwick and O'Connor 2013) and health equity (Loi et al 2013; Stapleton et al 2012), and to debates about the biological and the social, innate and acquired (Landecker and Panosfky 2013; Niewhoener 2015; Lock 2015; Meloni 2015;). In short, as a science that studies what lies beyond or above the genome and examines how the contingencies of life (pollution, stress, what we eat, etc.) affect how the genes operate, epigenetics has potentially paradigmatic implications for the biological and the social sciences, as well as for policy.

FRAMEWORK OF THE PROJECT AND HOW THIS THESIS DEVELOPED

This research is rooted in the "EPIGEN: Public Engagement and Policy Work on Epigenetics" (the EPIGEN project) which was initiated in 2013 to pursue the EPIGEN Consortium's commitment to integrate: 1) the study of Ethical, Legal and Social Issues within its research activities; and 2) the engagement of the public and policy makers on the implications of epigenomics more upstream in the research process. As the EPIGEN project itself stated:

> »This pioneering CNR-Flagship Project has recognized that the rise of high-throughput epigenomics, with its potential to revolutionize human health care, needs to take into account [the] fundamental changes in the ways in which science is being made accountable and responsive to societal needs and concerns. Therefore it has integrated the study of

> Ethical Legal and Social issues (ELSI) fully within its research activities, thus fulfilling EU's recommendation to consider ELSI as a critical component in the evaluation of risk for new technologies.» (EPIGEN: Public Engagement and Policy Work on Epigenetics)

To this end, the EPIGEN consortium established collaboration with the PhD programme of Foundations Of The Life Sciences And Their Ethical Consequences (FOLSATEC) at the European School of Molecular Medicine (SEMM) in Milan. The FOLSATEC PhD programme is opened to students with both scientific and philosophical background as it aims to create interdisciplinary scholars. The research projects of FOLSATEC students are developed during the course of their training and through their engagement with biomedicine and biomedical researchers in one of the following three areas: a) philosophical foundations of biomedicine and biotechnology; b) ethical implications of biomedicine and biotechnology; and c) biomedicine and society. In this respect, the programme represents an experimental and unique approach to the studies of biomedicine. Two FOLSATEC students were assigned to work on the EPIGEN project together with the principle investigator of the EPIGEN project, Prof. Testa: a student with a scientific background – myself, who had just enrolled in the FOLSATEC PhD programme; and Luca Chiapperino, a senior FOLSATEC student with a philosophical background.

This PhD project has thus been developed within the framework of the interdisciplinary PhD programme (FOLSATEC) and within the activities the EPIGEN Consortium's special Dissemination programme (EPIGEN project). This

study draws on ideas from the fields of philosophy of science, bioethics, public health, science and technology studies (STS) and political philosophy. It aims to deliver an empirically grounded interdisciplinary reflection upon epigenetics and its societal implications.

RESEARCH DESIGN AND METHODS

The initial aim of this project was to map the impact of epigenetics in health care and investigate the challenges of epigenetics for health care policy. The objectives of this research were:

1) To identify the most active types of epigenetics research – basic, translational, clinical research

2) To identify the most actively studied disease areas in each type of research

3) To identify the most active areas of application within clinical research

4) To identify the clinical outputs

The methods used in this part of the research project included systematic literature review, qualitative reading of literature, systematic review and qualitative reading of literature, and bibliometric analysis to track the record of publications on epigenetics/epigenomics. In order to position the results of this research in the broader picture of health care in Europe, the European Union (EU) Together for Health Strategy was used to identify the interests and goals in health management in the EU for that period (2008-2013). These interests and goals were further investigated in reports published by the World Health Organisation.

The succeeding objectives of this project were initially set as:

1) To investigate the onset of epigenomics by asking to what extent and how is the establishment of this health enterprise influenced by, on the one hand, developments in the life sciences to address complex diseases, and political commitments to tackle health inequities on the other. This objective was to be pursued within the framework of coproduction (Jasanoff, 2004) and by employing the concepts of boundary object (Star and Griesemer, 1989) and boundary work (Gieryn, 1983), to address how actors coming from different social worlds co-operate in a pursuit of a common goal, and create new and/or reinforce old divisions between fields of knowledge in pursuing their own research interests.
2) To develop a political framework for epigenetics-informed policy-making, by asking which values and goals should underlie our healthcare policy. This objective was to build upon Richard Rorty's ideas of postmodern pragmatism (Rorty 1983) to integrate different theoretical concepts which, in political philosophy, belong to different and often conflicting *theoretical* perspectives, but which could complement each other in *practice* to produce better policy-outcomes. The STS foundations of this framework would be grounded on Charles Thorpe's idea that STS offers tools and resources at the basis of which competing normative political visions of science and technology can be clarified, analysed and criticised – an idea which he himself referred to as 'STS as political theory' (Thorpe 2008). The descriptive framework would thus build upon the analytical tools and resources offered by STS, and would in turn give normative

power to the analyses conducted and the results obtained by using such tools.

Two key developments changed the shape of the research and this thesis. First, it became evident that the uptake of epigenetics in the broader discourse on inequalities in health is too sporadic and slow. It was noticeable in certain cohort studies and in several emerging projects and initiatives, but this was insufficient for a systematic data collection and analysis that was required of this project. The idea of looking in parallel at the life sciences and public health as fields was therefore changed into interviewing actors in these fields: the scientists a the IEO and within the EPIGEN consortium; and representatives of the World Health Organization (WHO) and the WHO for the European Region (WHO/Europe), who were invited to be speakers at the EPIGEN International Conference in Milan in December 2014. However, second and in relation to this new idea, the representatives of the WHO and the WHO/Europe declined their invitations to come to Milan and speak at the EPIGEN Conference. For this reason, the research further focused on one project that combined the life sciences and epidemiology in its approach to research and policy efforts for action upon health – the Glasgow-based psychological social and biological determinants of ill health (pSoBid) project. The pSoBid study report was at that moment the only document released by a health organisation (Glasgow Centre for Population Health) that contained a reference to epigenetic data. This therefore provided a unique opportunity to investigate not only how epigenetics is conceptualised by actors in different disciplines, but also how it is actually employed in health

policy. However, scaling down from the general to the local level reflected itself to the objectives that the project can pursue and research questions it can ask. Thus, the succeeding aim of this project was to explore how epigenetics is mobilised across domains by exploring how it is conceptualised by different actors in research and action upon health within one such interdisciplinary project. The research questions that the thesis asks include:

1) How is epigenetics mobilised and used in an interdisciplinary project that combines biological and social approaches to health?

2) How do different actors conceptualise and use epigenetics within a collaborative health endeavour aimed to bring about policy and action upon health?

The methods used in this part of research include qualitative reading of selected literature and semi-structured interviews with experts from the pSoBid project, complemented by observational studies. The study draws on ideas of molecularisation of the environment, biography and milieu (Landecker 2011; Niewöhner 2011); analogi-digital convertor (Meloni and Testa 2014); local biologies (Lock 2015; Niewöhner 2015) and solidarity (Prainsack and Buyx 2011; Prainsack and Buyx 2012; Rorty 1989).

Finally, scaling down from the general to the local level reflected itself also on the second initial objective, as the intended descriptive framework should have been located at the general level, not at the locally situated case of Glasgow. I attempted to correct for this by resorting back to a combination of quantitative and qualitative methods in examining values and concepts that inform normative discussions of societal implications of epigenetics. But this approach did not

yield results of sufficient quality to serve the original idea of the descriptive political framework, which would be used to 'compare, clarify and analyse' competing visions of health policy. Instead, the thesis opted to consider values and principles that were at play in the initiation and implementation of the collaborative approach to health and policy action in Glasgow.

A BRIEF OVERVIEW OF CHAPTERS

Following this introduction chapter, the thesis is first concerned with the *review of literature* upon which this project built. **Chapter 2** thus first outlines the science of epigenetics; it then moves to consider the societal implications of epigenetics; current governance of research; public health strategies and epigenetics; STS considerations of epigenetics; and finishes by outlining public representations of epigenetics. The review finds that empirical investigations of epigenetics in the current literature still occupy a much smaller corner than those of critical reflections upon epigenetics. This thesis therefore set to deliver an empirically grounded contribution to explorations of epigenetics and its societal implications.

Chapter 3 then moves on to describe *research design and methods* through which the data informing the conclusions of this thesis was gathered. The first section of this chapter describes a combined qualitative-quantitative srategy that was developed within this project to map the impact of epigenetics in health care and to track the number of publications on epigenetics. The second section then focuses on methods used to explore how epigenetics is mobilised and conceptualised by actors of diverse backgrounds in research and action upon

health. It describes how the field research in Glasgow with semi-structured interviews and observational studies was designed and conducted.

Chapter 4 draws on *empirical data* gathered through combined qualitative-quantitative strategy developed within this project to present the most active areas of epigenetic research, clinical application and clinical outputs; and to track the number of publications on epigenetics. It also presents data on how 'environment' is conceptualised/addressed in epigenomic practice; and on environmental epigenetics research and its commercial application. The chapter finds that epigenetics goes 'beyond the genome' insofar as what lies beyond can be converted into genome-friendly, code-compatible digital representations (Meloni and Testa 2014).

Chapter 5 draws on *empirical data* collected through semi-structured interviews and observational studies to discuss how molecularisation of the environment (Landecker 2011; Niewhoener 2011) is employed in research and health policy. It discusses collaboration among actors of diverse backgrounds in the pSoBid study; epigenetic data as 'evidence' in research and policy action; and communal identity and membership as the driving engine behind the pSoBid collective endeavour. The chapter finds that it is thanks to its molecularization of the environment and therefore its purported objectivity, that epigenetics is bestowed the potential for actionable public health knowledge in the Glasgow-based pSoBid project.

Finally, **Chapter 6** *concludes this thesis* by summarizing the findings and specifying the contribution of this research to the discussions on molecularisation of the environment, as well as on governance of research. The chapter and thesis finish with proposals for further research that include

exploring the epistemic and normative tensions and junstures that arise from understanding of the body as both universal and locally embedded by focusing on a regional (instead of local) network of researchers and institutions across the UK and Europe called EpiStressNet; employing gender analysis in research design and interdisciplinary dialogue in science and public debate; and exploring conceptual issues in epigenetic data collection and analysis in population studies, and their social dimensions.

A STATEMENT OF CONTRIBUTION

The four-year project (in further text, the PhD project) on which this thesis is based was partially funded by the Italian Epigenetics Consortium (EPIGEN Consortium). Such funding arrangement required a two-year collaboration on a related but distinct project (the EPIGEN project). This section therefore explains the nature and outputs of collaborations that took place throughout this PhD.

- The aim and objectives of the EPIGEN project have been set by its Principal Investigator (PI) Prof. Testa.
- The strategy for investigating the ethical, legal, and societal implications of epigenetics has been jointly devised by myself, a senior FOLSATEC colleague Luca Chiapperino, and our PhD supervisor Prof. Testa.
- All the empirical studies – for the EPIGEN project, and the PhD project that has been grounded in it – were deigned and conducted solely by myself. The results of these empirical studies have been shared with other members of the EPIGEN team. All work on the EPIGEN project was collectively presented in a White paper "EPIGENomics and Health Care

Policy: Challenges and Opportunities". This White paper was presented at the "EPIGEN International conference on EPIGENomics and Health Care Policy: Challenges and Opportunities" in December 2014, which was co-organised by myself, Luca Chiapperino, Prof. Testa, and Prof. Maccino (director of the EPIGEN Consortium).

- Due to my employment by the EPIGEN consortium to work on the EPIGEN project, this PhD project has been framed as 'epigenetics and policy'. Apart from this initial framing, this thesis has been composed solely by myself.
- The empirical study on Glasgow has been selected, designed and conducted solely by myself. Correspondingly, the data collected have also been analysed solely by myself. This can be verified with a report submitted to the funding body – the COST Action IS1001 – and its representatives – Andrew Webster and Bettina Bock Weulfingen – on November 28, 2014 – four weeks after my return from Glasgow; as well as with a 'Third year report' submitted to the PhD Graduate office in October, 2015, which was approved by my external advisor Barbara Prainsack.. The results of this empirical study have been shared with other members of the EPIGEN team.
- I am grateful to Kathryn Bouskill from Emory University who suggested me to have a look at Margaret Lock's work, after she heard my talk on "Gender and Epigenetics" at the Symposium "Body Discourse/Body Politics and Agency" February 6 2015 in Vienna (the paper was produced in collaboration with Anna Lydia Svalastog). The idea to explore the context of Glasgow through the concept of 'local biology' was later

discussed with Luca Chiapperino in a collegial exchange of opinions. This exchange resulted in a paper, co-authored by the EPIGEN team members. This co-authored paper awaits submission to the special issue on empirical studies of epigenetics of the journal Biosocieties under the title *The 'Glasgow effect': the political laboratory of localised biologies* by Damjanovicova, Chiapperino and Testa. Draft of this co-authored paper was presented at the 4S conference in Barcelona, September 2016. Additionally, the Glasgow study was presented at the ISHPSSB Conference in Montreal, July 2015 under the title *From Ants' Colonies to Working Classes: Molecular Epigenomics and the Digitization of Social Status* by Prof. Testa

The publications that resulted from this PhD include:

- Damjanovicova, M. 2016. Incidental findings. In: Boniolo G. - Sanchini V. (eds), *Ethical counseling and medical decision-making in the era of personalized medicine. A practice-oriented guide*, Springer International Publishing.
- Svalastog A. and Damjanovicova M. 2015. Epigenetics, society and bio-objects. *Croat Med J.* 2015; 56:166-8 doi: 10.3325/cmj.2015.56.166
- Damjanovicova M. 2014. Review of Boniolo, G. and Maugeri, P. (eds.): 2014, Etica alle frontiere della biomedicina. *Med Health Care and Philos* 2014; DOI 10.1007/s11019-014-9599-0

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CHAPTER TWO – LITERATURE REVIEW

INTRODUCTION

This chapter on literature review first outlines the science of epigenetics; it then moves to consider the societal implications of epigenetics; current governance of research; public health strategies and epigenetics; STS considerations of epigenetics; and finishes by outlining public representations of epigenetics.

THE SCIENCE OF EPIGENETICS

Epigenetics is an emerging science that studies changes in *gene expression* that do not involve changes to the *underlying DNA sequence*. The term epigenetics was coined by Conrad Waddington to define studies of the complex processes of how development of an *organism* is controlled by multiple genes:

> »Between genotype and phenotype, and connecting them to each other, there lies a whole complex of developmental processes. It is convenient to have a name for this complex: 'epigenotype'» (Waddington 1942).

David Nanney later defined 'epigenetic control system' as what determines which subsets of genetic specificities are to be expressed in a particular *cell* as epigenetic (Nanney 1958). Nanney's concept of 'epigenetic control' has been then applied in explaining cellular inheritance (Ephrussi 1958), somatic mutations in cancer (Luria 1960) and cellular differentiation (Abercrombie

1967). Epigenetics has thus developed two distinct 'traditions'. The Waddingtonian 'tradition' was concerned with causal processes by which genetic systems interact with the environment to bring about development and phenotypic plasticity. The Nanneyan 'tradition' was concerned with distinguishing between genetic and epigenetic causes of changes in cellular phenotype, including the transformation of somatic cells into cancer cells being (Haig 2012). The two 'traditions' have brought about a 'hybrid recombinant offspring' in recent years (cf. Haig 2012; Jablonka and Lamm 1989). Despite this 'hybridization of traditions', the multifarious origin of its meaning seem to have brought about a multitude of co-existing in-use *definitions* of epigenetics. Some of these definitions of epigenetics include:

- The study of »the mechanisms of temporal and spatial control of gene activity during the development of complex organisms» (Holliday 1990, 329);
- The study of the relationship between non-sequence-specific modifications of the genome and gene expression (Riddihough and Zahn 2010);
- The study of «any long-term change in gene function that persists even when the initial trigger is long gone that does not involve a change in gene sequence or structure» (McGowan and Szyf 2010, 67);
- The study of any «phenotypic variation that is not attributable to genetic variation» (Champagne 2010, 300);
- The study of »how signals from the environment trigger molecular biological changes (Powledge 2011, 588).
- The study of molecular changes «labile to environmental influence, which are important in regulating gene transcription and translation, and that create a self-

perpetuating, heritable, and reversible set of marks that determine how the genome in any given cell is expressed» (Landecker and Panofsky 2013, 337);

- The study of »mitotically and meiotically heritable changes in gene function that cannot be explained by changes in genetic sequence» (Allis et al. 2007, 16).

Most of these definitions are not subject of scientific debate, nor source of disagreement. The common use of the word 'epigenetics' in the current experimental practice relates mostly to the definitions proposed by Holliday (1990) and Riddihough and Zahn (2010), while the one of Landecker and Panofsky came to be endorsed in the fields of social, behavioural and environmental epigenetic studies. The last definition on the list, however, *is* disputed within the field. The problematic aspect of this formulation of epigenetics comes from its inclusion of 'meiotically heritable changes in gene expression', the existence of which polarises the field (e.g. see Iqbal *et al*. 2015; Guerrero-Bosagna 2016; Iqbal *et al*. 2016). The dominant opinion holds that epigenetic marks carried by the egg and sperm are erased after the fertilisation process, only to be established *de novo* in the embryo that is formed. Hence, epigenetics entails only mitotically heritable changes in gene expression, that is to say, within one generation. However, several studies demonstrated intergenerational (from parents to children) and transgenerational inheritance of epigenetic marks (from grandparents, and even before in the family tree, to grandchildren), which implies that these marks might, in fact, be meiotically heritable (e.g. Padmanabhan *et al*. 2013; Lambrot *et al*. 2013; Dias and Ressler 2014; Gapp *et al*. 2014a; 2014b).

Epigenetic *mechanisms* of gene regulation operate on different levels of nuclear organisation that include DNA sequence, histone proteins and nucleosome (the

basic unit of DNA packaging), and chromatin (the highest structure of the DNA-protein complex). In addition, non-coding RNAs also represent an epigenetic mechanism of gene regulation. The approximately 147 base-pair long strand of DNA is wrapped around a globular octameric core of four types of histone proteins (called H2A, H2B, H3, and H4; each of them comes in pair) to form a nucleosome – the basic unit of DNA packaging (Luger et al. 1997). Nucleosomes are connected between each other by another histone protein (H1, the linker histone), which results in formation of chromatin (Bernstein et al. 2007). The condensation of DNA in chromatin can very from loose – which makes the underlying DNA sequence available to transcription machinery – through intermediate levels of condensations that result in differential gene expression – to hypercondensation, which denies access to the underlying sequences and results in switching off of the underlying genes. Today's science of epigenetics is in large part concerned with studying modifications to which DNA or histone proteins are subjected, and the effects of those modifications on nucleosome, chromatin structure and, consequently, gene expression (Goldberg et al. 2007). The most characterized covalent (non-transient) modifications that can affect chromatin function include DNA methylation and post-translational histone modifications (Callinan and Feinberg 2006). DNA methylation occurs on the fifth position of the base cytosine (5mc) which is coupled with guanine (as CpG dinucleotides) and can be found in islands (1000-base pair long DNA stretches that are rich in CpG dinucleaotide and called CpG islands), transcription starting sites, gene bodies, as well as in other regulatory sites like enhancers or insulators. The discovery of 5-hydroxymethylcytosine (5hmC) as an intermediate of demethylation of 5mC to cytosine (Kriaucionis and Heintz, 2009;

Tahiliani et al., 2009) suggested DNA methyltion mark to be much more dynamic than previously thought. Instead of being quite a stable epigenetic mark as previously thought, DNA methylation seems to vary with context – the relationship between DNA methylation and transcription is more nuanced than was at first realized at first and its function thus seems to vary with context. A picture of DNA methylation as being diverse (in terms of its location and function) and dynamic (in terms its deposition and removal) emerged mainly thanks to the improvement of genome-scale mapping of methylation (Jones 2012; Rivera and Ren 2013). The three main ways to assay DNA methylation are digestion of genomic DNA with methyl-sensitive restriction enzymes; affinity-based enrichment of methylated DNA fragments (an antibody-capture based technique); and chemical conversion methods (Bock, 2012; Laird, 2010); each of which has its advantages and limitations (Rivera and Ren 2013).

Histone proteins are substrate of more than 130 covalent modifications that can be found on their tails and their globular domains. Histone modifications are involved in both activation and silencing of genomic regions, and can serve as binding substrates for recruitment or exclusion of proteins and protein complexes that serve different functions in different cell types (*ibid*.). Well-studied post-translational histone modifications (PTM) include acetylation, methylation, phosphorylation, ribosylation, ubiquitylation and sumoylation (Karlic et al. 2010) and are mostly found on amino acids lysine and arginine. Many novel histone PTMs are being unveiled by mass-spectrometry-based proteomic technologies (Tian et al. 2012). The role of these modifications is to change surface charge of histones, which in turn changes the overall strength of histone-histone and histone-DNA interactions. The main technique for mapping

the genome-wide binding pattern of chromatin-associated proteins, including modified histones, is chromatine immunoprecipitation (ChiP-seq), while mapping of chromatin structures is done by techniques that map nucleosome positioning and chromatin accessibility (Rivera and Ren 2013).

RNA-mediated mechanisms of gene expression have become regarded as epigenetic mechanisms, although some researchers have argued that they should not be considered as being epi-genetic since they do not regulate the expression of the genome, but rather affect processes of protein translation (Bernstein and Allis 2005). Noncoding RNAs were included among epigenetic mechanisms after their role in formation of "active" (euchromatic) or "silent" (heterochromatic) chromatin domains was discovered (Goldberg et al. 2007). The molecular basis of the crosstalk between RNA and chromatin, however, remains thus far unclear.

The last few years have been characterised by an overwhelming development in sequencing-based technologies: from whole genome sequencing, exome (messinger RNAs) and transcriptome (all RNAs) sequencing, to protein analysis and techniques for mapping various DNA and chromatin modification (e.g. ChiPseq, Ox-Bs-seq, MethylC-seq), as well as techniques for mapping the chromatin structure (e.g. DNase-seq, Hi-C). This overwhelming technological development made it possible to assay epigenetic modifications at the level of a *single* gene or modification, as well as to describe them across the *whole genome* (Callinan and Feinberg 2006). A *genome-wide* set of modifications made to DNA and the protein scaffold that supports it is called the 'epigenome' and the science that studies it 'epigenomics'. The science of *epigenomics* thus represents a «global, comprehensive view of sequence-independent processes [the

'epigenome'] that modulate gene expression patterns in a cell» (Rivera and Ren 2013, 39). Accordingly, the national and supranational project that aim to map these processes and produce 'high resolution' reference epigenome maps have been established in recent years: the NIH Roadmap Epigenomics Project in 2010; EpiGeneSys, Blueprint Epigenome in 2011; IHEC, EPIGEN and DEEP in 2012. These projects and consortia refer to the decoding of the human genome, and the subsequent acknowledgment that 'genes are not the only factors to regulate the many different functions of the human body'[2], as causing a shift in biomedical research towards the role that epigenetics has in this regulation. Results of one such consortium – the NIH Roadmap Epigenomics – were collectively published in across Nature Publishing Group journals in February 2015 (Roadmap Epigenomics Consortium 2015)

SOCIETAL IMPLICATIONS OF EPIGENETICS

The ethical, legal and societal implications of epigenetics have first been outlined by Rothstein, Cai and Merchant (2009). In this article, the legal issues of epigenetic findings were analyzed with respect to environmental regulation; food and drug regulation; litigation regarding harmful effects of chemicals and other environmental agents; occupational safety and health regulation; and discrimination in employment and health insurance. The ethical implications of epigenetics were discussed in relation to environmental justice, privacy and confidentiality, access to health care, intergenerational equity, and eugenics. The study concluded that 'numerous legal and ethical issues are raised by epigenetic'

[2] Available at http://www.deutsches-epigenom-programm.de/epigenomics/ (Last accessed on 12.12.2016.)

(*ibid*.). In a later paper, however, one of the authors claimed that even though some aspects of epigenetics raise interesting and challenging issues for ethics and law, "there is nothing inherently unique about the science of epigenetics that it demands an entirely new ethical paradigm and legal regime" (Rothstein 2013). Even without requiring an entirely new ethical and legal framework, investigations of epigenetics are contributing to normative debates on responsibility for health (Wiener 2010, Hedlund 2011, Chadwick and O'Connor 2013) and health equity (Loi et al 2013; Stapleton et al 2012). Moreover, its investigations may add to normative debates about the data management in biomedical research. Publicly available genomic databases have already been shown to put individual privacy at risk by allowing identifiability of the sample donor, and thus a potential exposure of some delicate personal information contained in the identified donor's sample (Gymrek et al 2013). The shift from single-gene towards the genome-wide approach has raised issues regarding the nature and scope of information that should be returned to research participants, as it makes possible to detect susceptibilities to certain conditions that may or may not ever develop into diseases (McEwen et al 2013; Damjanovicova 2016).

The epigenome-wide analyses probe samples from multiple tissues of any given individual and are coupled with genetic sequencing to determine the underlying genomic position of epigenetic marks in question (Pauline and Feinberg 2006, Marx 2012, Rivera and Ren 2013). In this respect, the issues of privacy and incidental findings may be further ignited because epigenomic information constitutes a further set of data from which genomic information can be drawn. However, the nature of epigenetic information may actually make a difference in

degree of the relevance of addressing potential issues related to privacy and incidental findings. Repositories of epigenetic information may reveal some very sensitive data, which would add up to sensitive genomic ones, like information of one's lifestyle and of health-related behaviours (Relton and Smith 2010). Such data enhance the richness of sole genomic information and have therefore the potential to make privacy breaches more detrimental (Rodenhiser and Mann 2006, Van Vliet et al. 2007). Moreover, the current clinical significance of some epigenetic modifications can often be uncertain and transient (Bernstein et al. 2010), making thus disclosure of this information questionable for its analytic and clinical utility.

The possibility to read the marks of environmental influences on one's body has the potential to make visible, in a molecular language, links between environmental exposures and health outcomes (Godfrey et al 2010; Gronniger et al 2010; Breitling et al 2011; Feil, and Fraga, 2011; Joubert et al. 2012; McGuinness et al 2012; Borghol et al 2012). The nature of this knowledge has important implications for epidemiological approaches to population health (Mill and Heijmans 2013; Relton and Smith 2010; Smith 2010; Michels 2012), as it may unravel the biological mechanisms through which the health prospects of a population are affected by unequal social arrangements (Loi et al 2013; Dupras et al 2012; Stapleton et al 2012). It has even been argued that epigenetics provides proof of principle of the health effects of socio-economic structures (Bateson et al 2004; Heijmans and Mill 2012). In this respect, the implication for health of both personal choices and collective decisions over environmental and social conditions could be made visible and knowledgeable by epigenetics. This

recognition may have some implications as to how responsibility for epigenetic changes should be allocated (Hedlund 2012; Chadwick and O'Connor 2013).

Moreover, molecular approaches to diseases have lead to revisionist efforts regarding the classification of diseases (Mirnezami et al 2012) and controversies over patenting and ownership of biotechnologies (Gostin 2013; Lenk, Hoppe and Andorno 2007), as well as regarding strategies for the validation and approval of new therapies (Mandrekar and Sargent 2009; Mahalatchimy et al 2012; Faulkner 2012). Epigenome modifying compounds (i.e. epidrugs), as well as epigenetically modified cells (Induced Pluripotent Stem Cells, iPSCs) for drug discovery contribute to debates on what counts as a disease, and how to best treat it (Brand 2001).

In short, the societal implications of epigenetics are to be regarded with respect to current debates about privacy and confidentiality; management of incidental findings; as well as to normative questions regarding individual and collective responsibility for health; and the governance of biomedical innovation. The bio-objectification framework (Vermeulen, Tamminen and Webster, eds. 2012; Melzer and Webster 2011; Gajovic 2014) and its employment in discussions about European policy and economy with respect to the value of bio-objects and the new bio-economies they produce (Maeseel et al 2013; Svalastog 2014) have been proposed as one direction in which the investigation of the societal implications of epigenetics can be furthered (Svalastog and Damjanovicova 2015).

THE GOVERNANCE OF RESEARCH

The European Union research policy has recently moved away from the study of ethical, legal and social issues (ELSI) of biomedicine as merely a critical component in the *evaluation* of the potential impact of scientific research. The cutting-edge approaches to science policy and scholarly research on the ELSI of scientific innovation have shifted towards more *inclusive approaches* to the governance of science. This has led to rethinking – as stated in the framework programme of Horizon 2020 – of the traditional linear model of innovation where the "societal challenges" of "excellent science" are treated as a second and separated step of the innovation pathway (European Commission 2013).

In anticipating this, the European Commission Directorate General for Research (DG-RTD) has in 2005 commissioned an inquiry on science and governance, focusing on: 1) how to respond to the widely-recognized problem of European public unease with science, especially in relation to new science-based technologies; 2) how to further the stated EU commitment to improve the involvement of diverse elements of democratic civil society in European science and governance; and 3) how at the same time to address urgent European policy challenges that are often taken as strongly scientific in nature – including climate change, sustainability, environment and development.

The result of this inquiry was a report "Taking European Knowledge Society Seriously" (European Commission 2007) which traced the evolution of EU Science policy and emphasized the transition from paradigm of Public Understanding of Science (PUS) to Public Engagement with Science (PES). Traditional PUS efforts assumed that public unease with science was largely the

result of a deficit in understanding on the side of the public (deficit model) and could thus be solved simply by enhancing scientific literacy. Yet, as documented in the report, ample evidence from empirical research, including 'rather unchanged outcomes of public surveys despite strong information/education campaigns', have prompted the policy and scientific communities to question the validity of the deficit model and endorse instead the paradigm of PES. In PES publics, including research participants, stakeholders and the potential consumers of new biomedical technologies, are not seen as downstream users who are simply in need of education, but rather as active citizens who can contribute to the production of new knowledge and have a legitimate interest in the modalities of its application. The rising involvement of stakeholders not simply in the funding of biomedical research but also in the shaping of its priorities and the distribution of its outcomes is an example of this new relationship between science and society in which 'interactions between scientists and lay persons build trust and mutual learning' and 'knowledge created in the laboratories is nourished by actions from citizens and mutual enrichment' (European Commission 2007).

From the sociology of scientific knowledge (SSK) towards Jasanoff's idiom of co-production, STS scholarship had been repeatedly signified that the production of knowledge and technology is a historical phenomenon, and that conceiving of alternatives within the routes of development of a given technology is feasible, as is acting politically to change the course of its development. In the words of Andy Stirling:

> «The form and orientation taken by science and technology are no longer seen as inevitable, unitary, and awaiting discovery in Nature[;] instead they are increasingly recognized to be open to individual creativity, collective ingenuity, economic priorities, cultural values, institutional interests, stakeholder negotiation, and the exercise of power» (Stirling 2008, 263).

The basis of technical decision-making thus can and should be opened up 'beyond the core of certified experts' (Collins and R. Evans 2002, 237). 'The 'democratization of expertise' was referred to as 'the order of the day in national governments and supra-national bodies such as the EU (Maasen and Weingart 2005, 2).

In analysing participatory programme of the British science policy, Thorpe suggested that such program 'has been explicitly oriented toward producing forms of social consciousness and activity seen as essential to a viable knowledge economy and consumer society' (Thorpe 2010) and argued that 'STS arguments for public engagement in science have gained influence insofar as they have intersected with the Third Way politics of post-Fordism' (Thorpe 2010; Thorpe and Gregory 2010). In following STS critiques of the liberal assumptions of science, Thorpe suggested that such critiques could be read from diverse perspectives: from communitarian and conservative philosophy, through Marxism and critical theory, to feminism and multiculturalism (Thorpe 2007). Accordingly, preoccupation in STS with questions of public participation and engagement in science were suggested to represent 'a turn toward participatory democratic and republican ideals of active citizenship' (Thorpe 2007). It has been argued, in fact, that democratic institutions should be grounded in a

conception of scientific and political representation instead of the prevailing 'liberal-rationalist' model (Brown 2009). In tracing the linkages between STS and political thought, Thorpe argued for a conception of STS as political theory:

> » STS *as* political theory offers a set of intellectual resources and models on the basis of which competing normative political visions of science and technology can be clarified, analyzed, and criticized» (Thorpe 2007, 64; original emphasis)

How such a conception could be put to work, however, remained opened to further exploration. Within political philosophy, Richard Rorty articulated the pragmatist position of John Dewey into what he called a 'postmodern pragmatism' whereby there are practical measures to be taken to accomplish a practical goal of bringing together concepts that are incommensurable at the level of theory (Rorty, 1983; 1989). In the article *Postmodernist Bourgeois Liberalism*, Rorty suggested that we should give up an account of rationality and morality as transcultural and ahistorical, while preserving our institutions (Rorty 1983). As there are no ahistorical underpinnings to these institutions, we can modify them to make them suit better this particular time in history. The most suitable concept upon which these institutions would then rest is suggested to be solidarity (*ibid*; Rorty 1989).

Solidarity has recently gained attention in writings on the governance of biomedicine. The Nuffield council on Bioethics commissioned an inquiry about solidarity as an emerging concept in bioethics. The report "Solidarity: reflections on an emerging concept in bioethics" (Prainsack and Buyx 2011) traced the

concept of solidarity from traditional approaches, like Roman Law, Christian wirings, or Marxist theories; to the more recent approaches of communitarianism, feminism, or contractarianism; and finally to recent bioethical literature. The authors offered a new approach to solidarity whereby solidarity signifies shared practices that reflect a collective commitment to carry 'costs' (financial, social, emotional or otherwise) to assist others. Being understood as 'a practice', solidarity therefore requires action (*ibid*.). Furthermore, solidarity is enacted at three-levels: personal, communal and contractual/legal (Prainsack and Buyx 2012). Accordingly, crises of solidarity are explained as occurring when inter-personal and communal levels of solidarity practices have 'broken away' while formal solidaristic arrangements continue to exist, as exemplified with welfare state arrangements (*ibid*.). In recent literature, solidarity has been discussed, for example, as an approach to the governance of biobanks (Prainsack and Buyx 2013) and in relation to lifestyle-related diseases and individual responsibility (Buyx and Prainsack 2012).

PUBLIC HEALTH STRATEGIES AND EPIGENETICS

One of the three core objectives set out by the first European Health Strategy was to 'Foster good Health in an Aging Europe' through Solidarity (EC 2007). In pursuing this objective, the Strategy advocated for prevention of health problems and disabilities from an early age through health promotion activities; and for tackling inequities in health linked to social, economic and environmental factors. The core principle on which such strategy is to be grounded is 'Health in All Policies' (HIAP). HiAP was initially used to designate

the main health theme of the Finnish Presidency in the European Union (EU) (Ståhl, Wismar, Ollila, Lehtinen and Leppo, eds. 2006), and has since been endorsed by many public health initiatives, both global and local, as an approach to, a strategy of, as well as a principle in health policy-making. The principle puts emphasis on the necessity for collaboration across different sectors that influence health, especially since greater socioeconomic inequality in society is associated with poorer average health[3] (cf. Ståhl, Wismar, Ollila, Lehtinen and Leppo, eds. 2006). The recently established European Partnership for improving health, equity and wellbeing – the EuroHealthNet[4] endorsed HiAP as its policy strategy[5] and set up a European portal for Action on Health Inequalities[6] within the Equity Action Project[7]. A global recognition of the HiAP approach came with the World Health Organisation's "Adelaide Statement on Health in All Policies: moving towards a shared governance for health and well-being" (WHO 2010).

Because of its emphasis on the relationship between the social and health gradient, the WHO Regional Office for Europe (WHO/Europe) introduces the HiAP principle and its Report in its 'social determinants of health section'[8]. There, poverty is indicated as a key factor in explaining poorer levels of health between the most and least well-off countries and population groups within the

[3] The papers cited include: Marmot M, Wilkinson R. Psychosocial and material pathways in the relation between income and health: a response to Lynch et al. British Medical Journal, 2001,322:1233–1236; Wilkinson R, Pickett K. Income inequality and population health: a review and explanation of evidence. Social Science and Medicine, 2006, 62:1768–1784; and Wilkinson R. Unhealthy societies: the affliction of inequality. London, Routledge, 1996.

[4] Available at: http://eurohealthnet.eu (Last accessed 12.12.2016.)

[5] Available at: http://www.health-inequalities.eu/HEALTHEQUITY/EN/policies/health_in_all_policies/ (Last accessed 12.12.2016.)

[6] Available at: http://www.health-inequalities.eu/HEALTHEQUITY/EN/home/ (Last accessed 12.12.2016.)

[7] Available at: http://www.equityaction-project.eu (Last accessed 12.12.2016.)

[8] Available at: http://www.euro.who.int/en/health-topics/health-determinants/social-determinants/publications/pre-2007/health-in-all-policies-prospects-and-potentials (Last accessed 12.12.2016.)

same country. Accordingly, the uneven distribution of social determinants leads to unfair and avoidable differences in health status across groups in society, i.e. to social inequities in health [9]. 'Inequalities in health' on the other hand, had its formal recognition as early as in 1978 with the Declaration of Alma Ata:

> «The existing gross inequality in the health status of the people particularly between developed and developing countries as well as within countries is politically, socially and economically unacceptable and is, therefore, of common concern to all countries» (WHO 1978)

Highlighting inequalities in health paved the way for the endorsement of 'health for all' principle of in the WHO Ottawa Charter for Health Promotion (WHO 1986). Accordingly, the WHO established a Commission on Social Determinants of Health in 2005, to support national and global efforts in addressing the social factors leading to ill health and health inequities and creating better social conditions for health, particularly among the most vulnerable people.[10] A few years later, the commission delivered a report "Closing the gap in a generation: Health equity through action on the social determinants of health" (WHO 2008). In this report, the city of Glasgow was highlighted as a region with both the healthiest and the least healthy population – its affluent citizens were at the top of the health list, while the socially deprived residents were at the bottom of this list, much behind all other regions including India and the black population in

[9] Available at: http://www.euro.who.int/en/health-topics/health-determinants/social-determinants/social-determinants (Last accessed 12.12.2016.)
[10] Available at: http://www.who.int/social_determinants/thecommission/en/ (Last accessed 12.12.2016.)

Washington DC. In the words of Sir Michael Marmot, chair of the WHO Commission on Social factors that determine health:

> «A boy in the deprived area of Calton had an average life expectancy of 54 years compared with a boy from affluent Lenzie, 12 km away in East Dunbartonshire, who could expect to live to 82» (WHO 2011).

Such epidemiologically severe urban profile of the city of Glasgow is not fully explained by conventional risk factors for disease as other equally deprived, former industrial cities of the UK (such as Liverpool, Manchester and Birmingham), which have faced similar effects of de-industrialization like Glasgow, have higher average life expectancies. These figures "earned" the city of Glasgow the reputation of 'the sick man of Europe', and led to the naming of this phenomenon: *the Glasgow effect* (*ibid*.).

The Report of the WHO Commission on Social Determinants of Health, however, concluded that it is possible to achieve health equity within one generation; that it is the right thing to do; and that now is the right time to do it. Accordingly, the Commission called for the WHO and all governments to lead the global action on social determinants of health for achieving health equity. These calls of the Commission have recently been formalised into a Political Declaration on Social Determinants of Health while the WHO Secretariat also devised a Global Plan of Action on Social Determinants of Health by[11]:

[11] Available at: http://www.who.int/social_determinants/action_sdh/en/ (Last accessed 12.12.2016.)

> «The declaration expresses global political commitment for the implementation of a social determinants of health approach to reduce health inequities and to achieve other global priorities»[12] (WHO 2011)

Two recent publications by the WHO Regional Office for Europe (WHO/Europe) resonate with these future commitments: the report on social determinants and the health divide in the European Region (WHO 2013a) and the follow-up of the first EU health strategy – the Health 2020 EU strategy for the twenty-first century (WHO 2013b). Both of these documents refer to the 'ample amount of evidence' collected on social determinants of health to recommend policies for reducing health inequalities. Director of the WHO/Europe, in fact, portrayed the Review as a 'wake-up' call to action among political and professional leaders (WHO 2013a, p. *v*). The EU Health 2020 strategy, on the other hand, adds that improving health for all and reducing health inequalities will be achieved 'through improved leadership and governance for health' (WHO 2013b). Likewise, as a reaction to the grim health figures reported in their city of Glasgow, the National Health Service Greater Glasgow and Clyde, the Glasgow City Council and the University of Glasgow, with the support from Scottish Government, established the Glasgow Centre for Population Health (GCPH)[13] to conduct research and propose policy actions to tackle health inequalities in Glasgow.

The (inverse) association between socio-economic circumstances and mortality from a wide range of diseases was first reported by the 1967 Whitehall study of

[12] Available at: http://www.who.int/sdhconference/declaration/en/ (Last accessed 12.12.2016.)
[13] Available at: http://www.gcph.co.uk (Last accessed: 12.12.2016.).

the British civil servants. Twenty years later, another cohort of civil servants, the Whitehall II study, was assembled in order to investigate the causes of the social gradient in morbidity (Marmot *et al*. 1991). The data from the Whitehall studies represent first pieces of empirical evidence on the existence of health inequalities and socioeconomic gradient in noncommunicable diseases. These studies paved the way for the establishment of social epidemiology – a discipline that systematically investigates the social determinants of health and disease (Chauvel and Leist 2015). Social epidemiology has recently started to include collection of the data also on epigenetic level. The life-course approach in population studies projects has particularly endorsed this trend, as exemplified by the LIFEPATH project (*Lifepath: healthy aging for all,* funded from the European Union's Horizon 2020 Research and Innovation Programme) – a life course population study that aims to investigate the biological pathways that underlie social differences in healthy ageing[14].

The challenges and opportunities of the synergy between epigenetics and epidemiology have first been highlighted by Karin Michels in *Epigenetic Epidemiology* (Michels, ed. 2012) – a book welcomed as 'a primer in epidemiology for epigeneticists and an epigenetics reference for epidemiologists' (Potter and Relton 2012). The International Journal of Epidemiology dedicated an entire issue to epigenetics in January 2012. Besides epigenetic epidemiology papers, the special issue of the International Journal of Epidemiology included reviews of epigenetics-related books and commentaries and opinions such as *Epigenetics: the next big thing* (Ebrahim 2012); *Is epidemiology ready for epigenetics?* (Relton and Smith 2012); and *Commentary: The seven plagues of*

[14] Available at: http://www.lifepathproject.eu (Last accessed 12.12.2016.)

epigenetic epidemiology (Mill and Heijmans 2012), or *Epigenetics for the masses: more than Audrey Hepburn and yellow mice?* (Davey Smith 2012). Considered together, these publications indicated that while many researchers embrace epigenetics in epidemiology, others are highly skeptical of its significance and utility. Despite such opposing perspectives, this type of research is experiencing a rapid growth. Some popular studies include associations between epigenetic markers and factors like socio-economic status (McGuinness et al 2012), smoking (Shenker et al 2013), air pollution (Baccarelli et al 2009), nutrition (Heijmans et al 2008), etc. reported in cohort studies like the Dutch Hunger Winter Families Study (Lumey et al 2007), the European Prospective Investigation into Cancer and Nutrition (EPIC; Riboli et al 2002), the Avon Longitudinal Study of Parents and Children (ALSPAC; Boyd et al. 2013; Fraser et al. 2013), or the psychological, biological and social determinants of ill health (pSoBid; Vellupilai et al 2008).

The pSoBid cohort was initiated by the GCPH as a cross-sectional, population-bases study which sought to examine population groups in Glasgow that differed in socioeconomic status and in their propensity to develop chronic disease (Vellupilai et al. 2008). The pSoBid cohort thus recruited participants from the most deprived and the most affluent Glaswegian communities. Results of the pSoBid study, were collectively presented in a document *Psychological, social and biological determinants of ill health (pSoBid) in Glasgow: a cross-sectional, population-based study: Final study report* which its proponents have thought as a guide for Glasgow's public health policies in the upcoming years (GCPH 2013). These include results of the studies on telomere attrition rate (Shiels et al 2011), levels of 25-Hydroxyvitamin D (Knox et al 2012), N-acetyl aspartate

concentrations (McLean et al 2012), the cerebellar grey matter volume (Cavanagh et al 2013), etc. as well as DNA methylation levels (McGuinness et al 2012). The pSoBid study Final Report therefore represents the first document published by a health organisation that refers to epigenetic data.

On the other hand, factors such as unhealthy diet, physical inactivity, tobacco use, the harmful use of alcohol, as well as ageing and rapid unplanned urbanization, are all listed as the factors that drive the development of noncommunicable diseases (WHO 2015 – Fact sheets). Noncommunicable diseases are reported as the leading causes of death both in developed and developing countries, representing thus the major burden in terms of disease contribution (WHO 2012). Since 2005 and after initial ten years of data collection, the WHO started with annual publication of the World Health Statistics. Its 'health forecast' for the next twenty-five years predicted a dramatic shift in the distribution of deaths from younger to older ages and from communicable to noncommunicable diseases (WHO 2006). Noncommunicable diseases were thus highlighted as 'a major health challenge of the 21st century', with cardiovascular diseases and cancer representing 48% and 21% of those deaths, respectively (WHO 2012).

Accordingly, the management of noncommunicable diseases (NDCs) is set as the global public health objective – the WHO Global Action Plan for the Prevention and Control of NCDs 2013-2020 (resolution WHA66.10)[15] was adopted at the 66th World Health Assembly. Moreover, this Global Action Plan on NCDs came after the United Nation (UN) Political Declaration on NCDs (resolution

[15] Available at http://www.who.int/nmh/events/ncd_action_plan/en/ (Last accessed 12.12.2016.)

A/RES/66/2)[16], adopted at the UN High-level Meeting on NCDs. The only other health issue, on which the UN General Assembly previously met, is acquired immune deficiency syndrome, AIDS). The strategy endorsed in addressing the problem of noncommunicable diseases is, accordingly, the HiAP strategy:

> «To lessen the impact of NCDs on individuals and society, a comprehensive approach is needed that requires all sectors, including health, finance, foreign affairs, education, agriculture, planning and others, to work together to reduce the risks associated with NCDs, as well as promote the interventions to prevent and control them» (WHO 2013).

STS CONSIDERATIONS OF EPIGENETICS

The STS engagements with epigenetics focus mostly on the subfield of epigenetics called environmental epigenetics, and its sociological (Landecker and Panofsky 2013), anthropological (Niewöhner 2011) and biopolitical implications (Mansfield 2012; Niewoener 2015). In biomedical practice, however, a variety of research approaches are gaining currency under the lemma of 'epigenetics'. The lack of an agreed precise definition of epigenetics was, on the one hand, suggested as enabling scientists from different disciplines to feel they are at the cutting edge of science as their work is 'epigenetic' (cf. Ebrahim 2012). The interviews with the cutting edge epigeneticists conducted by Martyn Pickersgill (2016) confirm such attitudes among the scientists, as epigenetics is considered a sexy term that tends to get people excited (Pickersgill 2016). Along the similar

[16] Available at http://www.who.int/nmh/events/un_ncd_summit2011/en/ (Last accessed 12.12.2016.)

line of reasoning, Meloni and Testa argued that the scientific success story of epigenetics lies precisely in 'the ambiguity of its very definition' (Meloni and Testa 2014), while Niewöhner evoked that the concept of gene, too, defied the attempts of an ell-encompassing definition and 'proved productive as an epistemic object of exquisite versatility capturing structural, functional and agential aspects of heredity, evolution and self-organization' (cf. Niewöhner 2011).

Environmental epigenetics research addresses the questions of 'how signals from the environment trigger molecular biological changes (Powledge 2011, 588). The environment, especially at early stages of life is considered as having a 'long-lasting impact on mental and physical health trajectories via epigenetic marking of specific genes' (McGowan and Szyf 2010, 71). Environmental epigenetics is thus part of a wider movement in the life sciences to incorporate 'matters social' into experimental, functional and mechanistic enquiry. Focusing on a particular and a rather small corner of biomedical endeavour is argued to offer a grasp on 'broader scientific and social transformations that might otherwise be hard to fathom or narrate' (Landecker 2011).

Drawing on ethnographic analysis of research practices of a particular lab that studies the effects of context on gene expression, Niewoeher argued that this style of doing epigenetic biology contributes to 'molecularisation of biography and milieu'; and suggested that such research practices produce a different concept of the body: the embedded body (Niewöhner 2011). Niewöhner's ethnography was centred in Moshe Szyf's epigenetics laboratory at the McGill University, Montreal Canada, which spearheaded the environmental epigenetics

(Weaver et al 2004). Niewöhner notes that although the practices, technologies and knowledge about cellular and molecular process in environmental epigenetics build on the dominant epigenetic genealogy, the theoretical agenda and experimental designs borrow from a much wider range of research (Niewöhner 2011). The environmental epigenetics is thus understood as bringing different levels of context into experimental designs of molecular and cellular biology. Contrary to the statistical significance sought in cancer research, the significance of findings in environmental epigenetics involves considering 'wider biology of the case in hand, as well as import of popular social theory to make plausible why certain instances of social change may lead to certain somatic changes' (Niewöhner 2011). The body that is being produced by environmental epigenetics is thus "heavily impregnated by its own past and by the social and material environment within which it dwells" (Niewöhner 2011, 11). Such understanding of socio-material environments and people's life-spans Niewöhner referred to as 'molecularisation of biography and milieu' – an extension of 'molecularisation of the environment' thesis proposed by Hannah Landecker (2011).

Focusing on the experimental formalisation of food, Landecker argued that such practices generate concepts of food as 'a form of molecular exposure' (*ibid*.). In the 'input-output' model of manipulation that dominates animal studies, epigenetics puts the focus on molecular events that occur between them. In such a model, food enters the body and never leaves it as 'it transforms the organism's being as much as the organism transforms it' (*ibid*. 177). Nutritional epigenetics thus proposes a specific molecular route of how things from the outside of the body are transformed into the biology of the body. The experimental

formalisation of food in nutritional epigenetics, according to Landecker, thus generates concepts of food as a form of molecular exposure and constitutes a molecular politics of eating (*ibid*.). The implication of 'molecularisation of the environment' should here be understood as a rearrangement of interrelation not a collapse of the inside and the outside. The divide between internal (nature) and external (nurture) has shaped the debate in health, education, and social policy in the last century, and corresponds to a significant political fracture between social conservatism and progressivism. In comparison with science wars on sociobiology and the excesses of genetic determinism, epigenetics looks, at least prima facie, a more promising and productive terrain of cooperation between biological research and sociology (Landecker and Panofsky 2013).

Accordingly, there is an ongoing interest in employing epigenetic bio-dosimeters (*ibid*; McGuinness 2012) for measurement in the social sciences and social epidemiology, and merging social sciences with epigenetics driven epidemiology and biomedicine (Niewoehener 2011; Meloni 2015). The measurement of the entire set of exposures – from environmental pollutants to work-related exposures, and lifestyles – to which individuals are subjected from conception onwards, throughout their lifespan, is in epigenetic epidemiology referred to as 'exposome' (Wild 2005, 2012; Vrijheid 2014). On the other hand, it has been argued that epigenetics promises to reduce the 'analogical vastness of the environmental signals' into 'genome-friendly, code-compatible digital representations' (Meloni and Testa 2014). In the words of Maurizio Meloni and Giuseppe Testa:

> »Epigenomic profiles, in their expanding variety, provide a new place holders to anchor the environment to the genome and enable the attending analogic-digital translations, conceptually as much as experimentally» (Meloni and Testa 2014, p. 6)

The evidentiary weight of *molecular* data has previously been shown with regards to exceptional status of DNA evidence in the present day courtroom (Lynch 2013) and the greater truth-governing power of genomic articulations of ancestry (Tall Bear 2013; Kent 2013). For example, in the course of the Innocence Project, original verdicts of over 250 prisoners in the U.S. were overturned through DNA testing or retesting from the bodily evidence collected during the original investigation (Lynch 2013). Similarly, states tend to privilege genome knowledge claims over, for example, the indigenous peoples knowledge claims when these are in conflict (Tall Bear 2013). Moreover, in some cases, the indigenous people were forced or have chosen to interact with genomic science for filing their claims, such as the case with DNA testing for tribal enrollment (Tall Bear 2013) or in disputed territory claims (Kent 2013). Critical reflections on epigenetics and race and ethnicity have also been offered (Kuzawa and Sweet 2008; Meloni 2015; Mansfield 2012; Mansfield and Guthman 2015).

Molecularisation of the environment is part of a broader 'molecularisation of biology' thesis (Rose 2001) and further extension of a 'molecular gaze' of the life sciences at different biological traits (Nowotny and Testa 2011). While the clinical body of the nineteenth century was located within a social body made up of extra-corporeal systems, the twentieth century genetic body is conceived on a different scale, as biology of the 1930s came to consider life phenomena at the

submicroscopic region (Rose 2001 p. 13). Molecularisation is therefore understood as an irreversible epistemological and a significant technical event. In the words of Nikolas Rose:

> »This molecularisation was not merely a matter of the use of artefacts fabricated at the molecular level. It was a reorganisation of the gaze of the life sciences, their institutions, procedures, instruments, spaces of operation and forms of capitalisation» (Rose 2001, p. 13).

As such transformations took place in the life sciences, biopolitics, according to Rose, has become 'molecular politics' (*ibid*). The advent of genetics and molecular understanding of life were argued to have caused a mutation in the way contemporary biopolitics operates. The target of biopolitics is no longer populations and their 'gross characteristics' such as race, but increasingly the individuals. Accordingly, interventions upon health do not take the form of 'normalisation' anymore, but instead take the form of 'optimisation' of one's own corporeality and psychology (Rose and Rabinow 2006). Epigenetics and molecular understanding of the environment was, instead, used to argue that contemporary biopolitics still targets the management of population, even if indirectly, via interventions on its 'gross characteristics' (Masfield 2009). In a paper *Race and the new epigenetic biopolitics of environmental health,* Mansfield focused on methylmercury contamination in fish as an environmental factor, and the efforts of regulatory agencies (Food and Drug Administration; and the US Environmental Agency) to control fetal exposures by issuing fish consumption advisories to women of childbearing age. According to Mansfield, these

advisories have greater impact on women of color due to existing racial disparities in fish consumption. Moreover, the advisories shift the problem from contamination itself to the inadequate diets of these women. The 'failure' of these women to make the right dietary choice is therefore understood as giving rise to bodily differences in people of allegedly different races.

In the words of Joerg Niewöhner:

> »Environmental epigenetic knowledge is equally readily adopted by those in favor of increasing social welfare spending and public health measures to reduce social inequality as it is by those in favor of increasing individualistic attention to early life development. The main biopolitical concern must therefore lie with the crude naturalization and subsequent reification of complex material-semiotic configurations inherent in both biopolitical positions.» (Niewöhner 2015, p. 224).

The concept of 'local biologies' has been suggested as a productive way to explore the promissory and precautionary narratives of epigenetics, as both a sociotechnical phenomenon and an interdisciplinary academic endeavour (Lock 2015, Niewöhner 2015). First used to describe the entanglement of subjective, socio-political and biomedical dimensions of menopause (Lock 1993; 2001), the approach of 'local biologies' showed how "it is appropriate to think of biology and culture as in a continuous feedback relationship of ongoing exchange, in which *both* are subject to variation" (Lock 2001, 503; original emphasis). Among the proponents of this concept as analytical tool for describing the social uptake of epigenetics, Jörg Niewöhner (2015) interpreted epigenetics as performing

subjectivities and social phenomena, as well as new materialisms and distinct understandings of the environment in its connections to the human body. Apart from the idea of 'temporary joint epistemic work' proposed to explain co-laboration around epigenetics between anthropologists and biologists who work on their own projects (*ibid*), collaboration between people of different backgrounds within one project working towards the same goal has been shown to depend on development of '*analytic concepts* of those scientific objects which inhabit several intersecting social worlds and satisfy the informational requirement of each of them'; that is to say, ' boundary objects', which are 'both plastic enough to adapt to local needs and the constraints of the several parties employing them, yet robust enough to maintain a common identity across sites" (Star & Griesemer, 1989; emphasis added)

REPRESENTATIONS OF EPIGENETICS IN POPULAR CULTURE

In January 2010, the Time magazine featured an article on epigenetics with a cover "Why your DNA is not your destiny. The new science of epigenetics reveals how the choices you make can change your genes – and those of your kids" (Cloud 2010). In the same year, the August cover of the German magazine Der Spiegel read *Victory over the gene – smarter, healthier, happier: how we can outsmart our genes* (der Sieg über der Gene - Klüger, gesünder, glücklicher: Wie wir unser Erbgut überlisten können), showing water wrapping around a prancing woman in the form of DNA double helix [17]. Ever since, the representations of epigenetics in popular culture have mostly consisted of

[17] Available at: http://www.spiegel.de/spiegel/print/d-73109479.html (Last accessed on 12.12.2016.)

sensationalistic stories about politically controversial and socially sensitive facets, as well as scientifically disputed research such as transgenerational inheritance in humans.

One such example is the Överkalix study, which has become something like a hallmark of epigenetic inheritance. In the section "Meet the Epigenome", the Time magazine article stated that »scientists have known about epigenetic marks since at least the 1970s. But until the late '90s, epigenetic phenomena were regarded as a sideshow to the main event, DNA. ... More recently, however, researchers have begun to realize that epigenetics could also help explain certain scientific mysteries that traditional genetics never could» (Cloud 2010). The 'mystery' considered in the Time Magazine article is data from the Överkalix study (Bygren et al 2001). The Överkalix study was conducted in the county of Norrbotten in Northern Sweden. It results of apparently made its author (Dr. Lars Olov Bygren, now at Karolinska Institute in Stockholm, but born and raised in the county of Norrbotten), «wonder whether ... parents' experiences early in their lives [could] somehow change the traits they passed to their offspring» (*ibid*.). The TIME Magazine article stated with confidence that «Bygren's data — along with those of many other scientists working separately over the past 20 years — have given birth to a new science called epigenetics"(*ibid*.)

In addition to making the headlines, the Överkalix study has been discussed on many blogs and forums, as well as in on-line educational courses on epigenetics, such as Coursera's *Epigenetic control of gene expression*[18]. A radio show called

[18] Available at: https://www.coursera.org/learn/epigenetics/lecture/7Y7Kz/5-5-human-epidemiological-studies-on-the-overkalix-cohort-grandparental-effects (Last accessed 12.12.2016.)

Radiolab[19] featured a podcast episode on Inheritance[20] featured an interview with Lars Olav Byrgen[21] and discussed the Överkalix study under the name "You are what your grandpa eats". The other two inheritance stories discussed in this podcast's were "Leaving your Lamarck" – about the early 20th century experiments of Paul Kammerer with midwife toads to prove Lamarckian inheritance, and the contemporary research of Michael Meanney and Frances Champagne on maternal care in rats[22]; and "What if there was no Destiny?" – about nature vs. nurture debate told through an adoptive vs. biological parents story[23].

With becoming the hallmark of *epigenetic* inheritance, or inheritance via *epigenetic mechanisms*, it would not be unreasonable to presume that some epigenetic data must have been collected on the Överkalix cohort. But this was not the case as the study used agricultural data and historical records of inhabitants in the nineteenth century. Unsurprisingly, biological samples from people who lived in the nineteenth century are not available. The Överkalix study, however, motivated further research as Dr. Byrgen joined forces with one of the prominent epigenetisists, Dr. Marcus Pembrey, involved in the Avon Longitudinal Study of Parents and Children (ALSPAC). Together with several other researchers, they published a paper on transgenerational inheritance in humans (Pembrey 2006), which the TIME Magazine article called 'the most compelling epigenetic study yet written' (Cloud 2010). However, not even this

[19] Available at: http://www.radiolab.org (Last accessed on 12.12.2016.)
[20] Available at http://www.radiolab.org/story/251876-inheritance/ (Last accessed on 12.12.2016.)
[21] Available at http://www.radiolab.org/story/251885-you-are-what-your-grandpa-eats/ (Last accessed on 12.12.2016.)
[22] Available at http://www.radiolab.org/story/251884-leaving-lamarck/ (Last accessed on 12.12.2016.)
[23] Available at http://www.radiolab.org/story/251887-what-if-no-destiny/ (Last accessed on 12.12.2016.)

study actually conducted research on epigenetics, although biological samples for the ALSPAC cohort are available (Boyd et al. 2013; Fraser et al. 2013).

Another study that has become a hallmark of epigenetic inheritance is the study on the effects of maternal behaviour on offspring (Weaver et al 2004). The Discover Magazine featured an article about this study "Grandma's Experiences Leave a Mark on Your Genes" (Hurley 2013). Other studies on transgenerational epigenetic inheritance include The Economist magazine "Poisoned inheritance"[24] about a diet-induced sperm reprogramming in mice (Lambrot et al. 2013) and The Scientist magazine "Upside of early life stress?"[25] about early life stress in fathers inducing behavioural flexibility in their offspring (Gapp et al. 2014); etc.

Inheritance and early-life exposures are also the central topic of popular books on epigenetics. Nessa Carey's "The Epigenetisc Revolution: How Modern Biology is Rewriting Our Understanding of Genetics, Disease and Inheritance" (Carey 2011) was praised by her scientist colleagues as providing a great basic introduction to the topic of epigenetics, as well as a sense of the challenges and opportunities it presents. Yet, the book also offered an epigenetic account of life of 'a film and fashion icon' Audrey Hepburn. Hepburn was exposed to the so-called Dutch Hunger Winter[26] when she was a teenager, which in the book is offered as an explanation of Hepburn's 'fragile health' in adulthood. Some studies have investigated the links between effects of Dutch Huger Winter and health

[24] Available at http://www.economist.com/news/science-and-technology/21591547-lack-folate-diet-male-mice-reprograms-their-sperm-ways (Last accessed on 12.12.2016.)
[25] (Last accessed on 12.12.2016.) http://www.the-scientist.com/?articles.view/articleNo/41465/title/Upside-of-Early-Life-Stress-/ (Last accessed on 12.12.2016.)
[26] The Dutch Hunger Winter refers to the period during the WWII in which the Netherlands' food supply was blocked by the Nazi's, causing an extreme hunger

outcomes via epigenetics, like The Dutch Famine Birth cohort study[27]. These studies focus on the effects experienced *in utero*, and their health consequences experienced in adulthood. Audrey Hepburn did not, and was not eligible to, participate in such studies, as she was a teenager at the time when the environmental insults occurred.

Other popular accounts on epigenetics by scientists, such as Spector's "Identically Different: Why you can change your genes" focus, as indicated by the book's title, on our ability to change our genes (Spector 2012). Outside the popularising accounts of epigenetics offered by scientists, a genre of 'biology of belief' or 'biology of intention' is also increasingly engaging with epigenetics, with "The Genie in Your Genes: Epigenetic Medicine and the New Biology of Intention" being its original and still most popular example (Church 2007).

EPIGENETICS AND POLICY – THE THESIS

One of the most intriguing features of epigenetics has been its capacity to be mobilized in a variety of fields beyond biomedicine, most notably the social sciences. It has been welcomed as a healthy opportunity for cooperation between disciplines that in the past have animated cultural wars – with a political undertone – as for the respective place of innate (nature) and acquired (nurture) traits (Landecker and Panofsky 2013). It constitutes an object of inquiry for anthropology and social sciences, engaging them with a molecular understanding of cultural and social practices (Landecker 2011, Landecker and Panofsky 2013). At a meta-disciplinary level, epigenetics prompts reflections on

[27] Available at: http://www.dutchfamine.nl/index_files/study.htm (Last accessed 29.08.2016)

the very boundaries between social and natural sciences, and the opportunities and challenges entailed in constructing mixed epistemic categories (Meloni 2015). It also holds the potential to "both propel sociotechnical change and (co-)produce novel conceptualisations of biosocial entities" (Pickersgill et al. 2013, 438). The transdisciplinary success of epigenetics seems to be predicated upon the intersection of its theoretical significance, social promises and amenability to inquiry.

Yet, the empirical investigations of epigenetics in the current literature occupy a much smaller corner than those of critical reflections upon epigenetics. This PhD project delivers an empirically grounded contribution to explorations of epigenetics. In particular, by focusing on the case of Glasgow, a city characterized by stark health and social inequalities, where epigenetics has been employed in a interdisciplinary project to measure and instruct relevant social programs to target these inequalities, this thesis contributes a critical insight into how epigenetics is currently employed – in collaboration between actors of diverse backgrounds; and in policy efforts and action upon health. Being grounded in a programme of interdisciplinary character, this thesis contributes a meta-disciplinary reflection on epigenetics and its societal implications.

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CHAPTER THREE – RESEARCH DESIGN AND METHODS

INTRODUCTION

This chapter describes the methods through which the data informing the conclusions of this project was gathered. The chapter is divided into two sections according to the two separate aims of this project. Section one is concerned with methods employed in pursuing the aim of mapping the impact of epigenetics in health care. The section first describes how the research was designed; it then moves to the materials and methods used in collecting the data; the rational behind using those methods; and the techniques of data analyses in each of the studies that were conducted. Section two is concerned with methods employed in pursuing the aim of exploring how epigenetics is conceptualised by actors of diverse backgrounds in research and action upon health. The section first describes how the research was designed and the rational for using semi-structured interviews as methods for data collection; it then addresses the challenges that arose and the techniques and processes of data analysis; and finishes with notes on ethics and reflexivity.

MAPPING THE IMPACT OF EPIGENETICS IN HEALTH CARE

Research design

The initial and primary aim of this project was to map the impact of epigenetics in health care. This aim was driven by the need to accomplish the tasks for the

EPIGEN project assigned to me by the EPIGEN team. The objectives of this research were:

1) To identify the most active types of epigenetics research (basic, translational, clinical research)

2) To identify the most actively studied disease areas in each type of epigenetic research

3) To identify the most active areas of application within clinical epigenetic research

4) To identify the clinical outputs of epigenetics

The methods used in this part of the research project include qualitative reading of literature; systematic literature review; systematic review and qualitative analysis of literature; and bibliometric analysis to track the record of publications on epigenetics/epigenomics. Moreover, in order to position the results of this research in the broader picture of health care strategies in Europe, the European Union (EU) Together for Health Strategy was used to identify the interests and goals in health management (EC 2007). These interests and goals were further investigated in the reports published by the World Health Organisation (WHO 2006; 2008; 2011a; 2011b; 2012; 2013a; 2013b; 2015).

All the studies in this part of the project were conducted twice – once in 2013 and once in 2014. The rationale behind repeating the studies was reproducibility of the results obtained, hence, after the first round of results in 2013, another round of studies had to be conducted in the following year. The results collected in 2013 were presented at the EPIGEN annual meetng in Rome, February 2014.

The results collected in 2014 were presented at the EPIGEN International Conference on "EPIGENomics and Health Care Policy: Challenges and Opportunities" in Milan, December 2014.

PubMed generated systematic literature review

Materials and methods

The data area used in pursuing the first two objectives from the list above was biomedical literature. The database used in these queries was PuBMed. PubMed database was selected because my colleagues from labs at the European Institute of Oncology in Milan indicated it as the most commonly used database in biomedical practice. Thus, the PubMed database seemed like the most proper choice for conducting research on biomedical literature. A quantitative approach to data collection was an obvious choice for pursuing these objectives. In social studies of science, quantitative approaches usually entail network analysis (e.g., Cambrosio et al 2006; Navon and Schwed 2012) whereby networks of interactions among actors and groups can be identified. Applying this method, however, would not allow for teasing out the information sought after by the specific tasks that required by the EPIGEN project. A combined quantitative-qualitative analytical strategy was proposed by Heur at al (2013) in their examination of evidence for the claim of 'ontological turn' in STS. In this article, quantitative analysis of the social science and humanities journals and a subset of STS literature were combined with bibliometric tools to analyse network structures in the social and knowledge relationships in the STS subset, and with qualitative reading of this literature. Following this strategy proposal (Heur at al

2013), a combination of quantitative analysis with qualitative reading of literature, without the bibliometric analysis of this literature, was selected as the protocol to be followed in this research. The bibliometric analysis was skipped in this research, as the specific questions asked by the EPIGEN project did not require this kind of analysis.

In conducting the systematic review, the following parameters of the PubMed database were kept constant across all searches:

1) Text availability – full text
2) Species – humans
3) Languages – English
4) Article type – reviews and systematic reviews.

In the pilot phase of the study, the 'article type' parameter of the PubMed database varied and it was set to: 1) all types of articles; 2) reviews; 3) reviews and systematic reviews; and 4) systematic reviews. The 'reviews and systematic reviews' was selected for further research as a representative enough of the general field while reducing the number of papers to be subjected to qualitative assessments. A qualitative reading of papers produced by 'all types of articles' search would not be manageable for one person. The specific combinations of search terms that were used for in this systematic review are shown in Table 1. Moreover, the pilot study also performed the searches by using both 'epigenetics' and 'epigenomics' as search terms. 'Epigenetic' was selected as the more exhaustive and relevant term for further studies.

Type of research / Disease area	Epigenetics	Epigenetics, Treatment	Epigenetics, Treatment, Clinical trial
Cancer			
Cardiovascular diseases (CVDs)			
Neurodegenerative diseases (NDDs)			
Autoimmune diseases (AIDs)			
Diabetes			

Table 1: A grid of standardised search terms used in the systematic review of biomedical literature

Data analysis

Data analysis included recording and combining of the data collected into different tables designed in Microsoft Excel program; and then visualising the results using Excel tools. The overall results of these searches are shown in Table 2, while the graphs that visualise the results can be found in Chapter Four – Beyond The Genome.

The 'type of research' area was processed in the following way:

1) The results of searches that contained a combination of terms 'epigenetics' and 'treatment' were taken as being representative of 'translational research' in epigenetics.
2) The results of searches that contained a combination of terms 'epigenetics', 'treatment' and 'clinical trial' were taken as being representative of 'clinical research' in epigenetics.
3) These results on 'translational research' and clinical research' were subtracted from the results of searches that used only 'epigenetics' as a search term, and were taken as being representative of 'basic research' in epigenetics. In other words, of all epigenetic research, the part that was neither translational nor clinical was taken as being representative of 'basic research' in epigenetics.

Key words	No. of papers
Epigenetics	2557
Epigenetics, treatment	947
Epigenetics, treatment, clinical trial	42
Epigenetics, CANCER	1088
Epigenetics, treatment, CANCER	560
Epigenetics, treatment, clinical trial, CANCER	31
Epigenetics, CVDs	163
Epigenetics, treatment, CVDs	80
Epigenetics, treatment, clinical trial, CVDs	4
Epigenetics, NDDs	104
Epigenetics, treatment, NDDs	41
Epigenetics, treatment, clinical trial, NDDs	3
Epigenetics, AIDs	106
Epigenetics, treatment, AIDs	36
Epigenetics, treatment, clinical trial, AIDs	2
Epigenetics, Diabetes	40
Epigenetics, treatment, Diabetes	16

Epigenetics, treatment, clinical trial, Diabetes	1

Table 2: Systematic review of biomedical literature

Systematic review and qualitative analysis of the clinical research and application of epigenetics

Materials and methods

The 'clinical research in cancer' results (produced by a combination of 'epigenetics, 'treatment' and clinical trial' as search terms) were qualitatively analysed to identify the most targeted epigenome-modifying processes (or mechanisms) in clinical research. The rational behind conducting this qualitative analysis was that searching for 'epigenetics' in the clinical trials repositories (the NIH National Cancer Institute, NCI and the European Union Clinical Trial Register, EU-CT) did not yield any results. It is, however, known that several epigenome-modifying compounds received market authorisation and many are being clinically tested. Therefore, generating more fine-grained search terms was necessary in order to perform further investigation of the areas of application within clinical epigenetic research. Table 3 shows the results of this qualitative analysis.

The rational for focusing on cancer was two-fold. First, cancer scored as the most studied disease area in all types of research presenting thus an obvious choice as a case study of further investigation. Second, the results of clinical trials (CT) used specific names for compounds that were being tested, separately or in combination with other compounds, and not the mechanism of their action.

Search terms: epigenetics, treatment, clinical trial, cancer	
Total No. of papers	31
DNMT related papers	5
HDAC related papers	8
DNMT and HDAC papers	11
Other mechanisms papers	7

Table 3: The most targeted mechanisms of epigenome-modification in clinical epigenetic research

Moreover, some CTs referred to epigenome-modifying compounds only in order to discuss the compound that was actually tested in the trial at hand. A qualitative reading of all the clinical trials reported in the results was therefore required to confirm that the CTs reported in the results were actually being conducted on an epigenome-modifier. Analyzing the results of all clinical trials on epigenome-modifiers for all types of diseases was a task beyond the abilities of one person. Thus, even though it itself produced a substantial number of CTs to be subjected for qualitative reading, cancer was selected as a case study for identifying the most active areas of application of epigenetics in clinical research. Further studies conducted in the NCI and the EU-CT online database of clinical trials thus used the following two search terms: 1) histone deacetylase; and 2) methyltransferase.

In a pilot study, the search terms used where 'histon deacetylase inhibitor' and 'methyltransferase inhibitors', because their mechanism of action on the epigenome is inhibition. However, the combination of epigenetics-related search terms (histone deacetylase and methyltransferase) with the term' inhibitor' produced an unexpectedly large number of results, suggesting that all clinical

trials containing a term 'inhibitor' were reported in the list of results. The qualitative reading of the results confirmed that this was, indeed, the case. Therefore, the search was repeated with using only terms 'histone deacetylase' and 'methyltransferase' as key words. Table 4 and Table 5 show the data collections in these searches, respectively, which were submitted to qualitative reading to confirm the results were addressing the questions asked. The results that were generated were then used to compile a list of currently studied epigenome-modifying compounds. Finally, each of the compounds from this list was searched for in the US Food and Drug Administration (FDA) database and the European Medicinal Agency (EMA) database to examine whether the compound has already been approved and for what kid of application. The results of this study are shown in Table 10 in Chapter 4.

HISTONE DEACETYLASE	All phases of CT		
	Actively recruiting	Not recruiting	Total No.
All CT	174	249	423
Treatment	166	235	401
Supportive care	4	3	7
Screening	1	0	1
Prevention	2	2	4
Genetics	0	0	0
Diagnostic	5	2	7
Biomarker/laboratory analysis	76	121	197
Tissue collection/repository	1	2	3
Education/counselling/training	0	0	0
Behavioural study	0	0	0
Natural history/epidemiology	1	0	1
Health services research	1	0	1

Table 4: On-going clinical trials on histone deacetylases as targets of epigenome modifying compounds in cancer

METHYLTRANSFERASE	All phases of CT		
	Actively recruiting	Not recruiting	Total No.
All CT	45	47	92
Treatment	35	45	80
Supportive care	3	1	4
Screening	0	0	0
Prevention	3	1	4
Genetics	0	0	0
Diagnostic	1	1	2
Biomarker/laboratory analysis	28	14	42
Tissue collection/repository	0	0	0
Education/counselling/training	1	0	1
Behavioural study	1	0	1
Natural history/epidemiology	1	0	1
Health services research	1	0	1

Table 5: On-going clinical trials on methyltransferases as targets of epigenome modifying compounds in cancer

Data analysis

Data analysis included recording and combining all collected data into different tables designed in Microsoft Excel program; and then visualising the results using Excel tools. The results of this activity are shown in Table 4 and Table 5, while the graphs that visualise the results can be found shown in Chapter Four – Beyond The Genome.

The type of application in clinical research shown in Table 4 and Table 5 were limited by the parameters for 'type of trial' set by the NCI database itself. Based on these parameters, type of application in clinical research in cancer include: 1) all types of CTs; 2) treatment; 3) supportive care; 4) screening; 5) prevention; 6) genetics; 7) diagnostic; 8) biomarker/laboratory analysis; 9) tissue

collection/repository; 10) education/counselling/training; 11) behavioural study; 12) natural history/epidemiology; and 13) health services research.

Additional research task for the EPIGEN project

Bibliometric analysis to track the record of publications on epigenetics/epigenomics

This study was conducted as an additional task assigned to me by the EPIGEN team. The aim of this study was to examine the claims that there is an exponential increase in the number of publications carrying 'epigenetics' in their title (Haig 2012), reaching several thousands, possibly even up to 20 000 by 2011 depending on the search criteria (Jirtle, 2012) by producing a new method to track the number of publications on epigenetics/epigenomics. The working hypothesis of the EPIGEN project was that while these claims are true, the numbers are most likely exaggerated. The claim about the increase therefore needed to be substantiated by numbers obtained through systematic investigation that could then be shown to the decision-makers, which the EPIGEN project and its White paper aimed to reach. The method used in this analysis was thus tailored for the specific purpose of this study. The study was first performed using PubMed as a source but was later refined by using the webpages of selected biomedical journals as a source. The reason behind the switch of sources is that PubMed reports results for the text deposited in it, which in some cases means only the abstract of papers and not their full content. Journals' webpages, although denying access to the full text for reading, store the

full text in their database. Their results would therefore report more accurately the number of publications that contain epigenetics/epigenomics.

PubMed searches: The search terms used in probing this database were: 1) epigenetic; 2) epigenomics; epigenetic/epigenomic; 3) epigenetics, epigenetics/epigenomics, 4) epigenomic; epigenetics/epigenomics; and 5) epigenetics, epigenetics/epigenomics, epigenomics. The search parameters of the database were set to 'text word' and 'English'. The searches were conducted for the years 2008, 2009, 2010, 2011, 2012, and 2013 (the year in which the study was conducted). The journals included in the searches were: Nature, Nature Biotechnology, Nature Cell Biology, Nature Communication, Nature Genetics, Nature Immunology, Nature Medicine, Nature Methods, Nature Neuroscience, Nature Protocols, Nature Reviews [Cancer, Cardiology, Clinical Oncology, Drug Discovery, Endocrinology, Gastroenterology & Hepatology, Genetics, Immunology, Microbiology, Molecular Cell Biology, Nephrology, Neurology, Neuroscience, Rheumatology, Urology]; Science, Science Signalling, Science Translational Medicine; Cell, American Journal of Human Genetics, Biophysical Journal, Cancer Cell, Cell Host & Microbe, Cell Metabolism, Cell Reports, Cell Stem Cell, Chemistry & Biology, Current Biology, Developmental Cell, Immunity, Molecular Cell, Neuron, Stem Cell Reports, Structure; PLoS Biology, PLoS computational Biology PLoS Genetics, PLoS Medicine, PLoS One; EMBO, EMBO Reports, Blood, NEJM, The Lancet, The Lancet Diabetes & Endocrinology, The Lancet Global Health, The Lancet Neurology, The Lancet Oncology, The Lancet Respiratory Medicine; and British Medical Journal. Additionally, the same search was repeated with search terms 'genetic/genomic'

instead of 'epigenetic/epigenomic' to control for the contamination of the results by the underlying 'genetic/genomic' part in 'epigenetic/epigenomic' terms.
The rational behind selecting these journals and a five-year span was that these journals are reported as the top 65 scientific journals in the years 2012 based on their 5-year impact factor by *ISI Web of Knowledge 5-year Journal Impact Factors lis*t of Thompson and Reuters[28];

***Journals' webpages searches**:* These searches were meant to prevent the "information loss" that was experienced through the PubMed database mining. However, the challenge arose in standardisation of search terms that would be used across webpages of all journals targeted in the study. This challenge arose due to differences in options that different journals provide for search-fields and/or for combining search terms. Namely, some pages of some journals', such as BMJ, allow for combining of terms in the same search but report 'no results found' for such search; while when searches are conducted using any one of the terms from this combination, the results appear. Therefore, in order to conduct a systematic investigation, the searches had to be conducted in a term-by-term fashion for each of the journals (or journal group, such as Nature Publishing Group) for the list: 1) a separate search for the term 'epigenetics'; 2) a separate search for the term 'epigenetic'; 3) a separate search for the term 'epigenomics'; and 4) a separate search for the term 'epigenomic'.

[28] The data were collected under conditions of free-access to the database of WoK. These conditions are no longer available, probably due to some recently occurring restrictions to website access.

Data analysis

Each of the four separate searches was conducted for each of the journals in the list presented above, and for each of the years (2008-2013). The search results for every consecutive page that appeared were opened in a 'page source' option of the browser; the text for every page was copied and saved into a word document in a consecutive manner. The files of each of the search terms were then combined into a single file, and correspondingly so, for every journal in every year. This activity produced thus a series of files like this: Nature 2008; Nature 2009; Nature 2010; Nature 2011; Nature 2012; Nature 2013; EMBO 2008; EMBO 2009; EMBO 2010; EMBO 2011; EMBO 2012; EMBO 2013; etc. for each of the journals and years. All together, this search generated sixty data files.

In order to control for the potential doubles in these results, I consulted a colleague with highly developed computational skills, Dr. Pierre-Luc Germain, about how to write a code in Python programming language that would count how many of the titles in each of these sixty files are unique. This code would thus help in eliminating the titles that could appear more than once in these files, when both 'epigenetics' and 'epigenomics' would appear in the same publication. As the searches were conducted for each of these terms separately, such publications would be counted twice without a script/code to control and correct for this. The data that were collected were then inserted into a Microsoft Excel table and visualised into graph using Excel tools. An example of how these results were formatted to be quantifiable is shown in Table 6 (for the years 2008 and 2012).

Journals	2008 publications			2012 publications		
	Total No.	Script No.	Unique No. (script derived)	Total No.	Script No.	Unique No. (script derived
Nature(s)	542	540	417	989	984	734
Science(s)	71	71	61	209	209	174
Cell(s)	415	369	331	853	715	587
PloS(s)	500	620	234	2768	2768	1277
EMBO(s)	76	76	61	117	117	91
Blood	120	120	106	218	218	184
NEJM	46	46	20	40	40	19
Lancet(s)	26	25	24	40	40	38
JAMA	38	80	20	20	80	20
BMJ(s)	5	5	4	10	9	8
Total number	1839	1952	1278	5264	5180	3132

Table 6. Bibliometric analysis to track the record of publications on epigenetics/epigenomics

Additional materials and their analysis

Qualitative analysis of selected life sciences literature

The data used in this analysis are the collectively released results of the NIH Roadmap Epigenomics project published in the special issue of the journal *Nature* in February 2015. The rational behind focusing on the NIH Roadmap Epigenomics results is two-fold. First, the quantitative-qualitative analyses conducted for the EPIGEN project were not designed to address how is 'environment' conceptualised in epigenetic research. Yet, environmental epigenetics and molecularisation of the environment are precisely the areas of epigenetic research that gain most attention in different domains beyond biomedicine. Conducting another qualitative-qualitative study with tailored search terms and methodology to address this was not plausible, due to time

constraints of the PhD programme and project. Therefore, a small-scale research had to be selected instead. Second, within the five initiatives of the Roadmap Epigenomics project, one includes research on responses to exposures like physical, chemical, behavioural and social factors. Other big epigenetic consortia also state that understanding how environment influences human health and populations is among their projects' main objectives. Such statements are made on projects' description pages and as such are intended for the general and interested public. The published data of these big consortia are, instead, intended for the research community, where they also set the aims and norms of current and future research. Their analysis could therefore indicate to what extent and how is environment actually conceptualised in wider research community. Each of the papers was reviewed in search for: 1) whether the words 'environment' or 'environmental' occur and how often; and 2) if the research makes at least a general reference to anything else besides the intra-cellular components that could be remotely related to the extra-cellular, extra-organismal factors.

Qualitative reading of documents published by the regional and global health authorities

The first European Health Strategy "Together for Health" was used to identify: 1) the challenges that the EU recognises as priorities to be addressed in the upcoming years; 2) the principles on which the health strategy for the future is grounded; and 3) the values that drive its implementation. The rational for this analysis was to explore how the impact of epigenetics in health care, mapped in

this project, fits with health challenges identified by European authorities and strategies to address them. The health challenges reported in the EU health strategy were further explored in documents published by the WHO and include: complex diseases and health divide, i.e. inequalities in health. Within 'inequalities in health' theme, the 'social determinants of health approach' was further explored for two reasons. First, poverty was reported as the main factor that leads to poor health. Second, the case study of this project – the psychological, social and biological determinants of ill health (pSoBid) project – investigated epigenetics in relation to socio-economic status.

Exploring how is epigenetics represented in the public

Occasional searches in Google were conducted and epigenetics-related content on these pages was reviewed for what type of studies and research they covered. Additionally, biomedical journals were monitored for discussions regarding media representation of epigenetics.

EXPLORING HOW EPIGENETICS IS MOBILIZED ACROSS DOMAINS AND CONCEPTUALIZED BY DIFFERENT ACTORS IN RESEARCH AND ACTION UPON HEALTH

Research design

For exploring how epigenetics is mobilised across domains and conceptualised by actors of diverse backgrounds in research and action upon health, the

research focused on one particular case – the psychological, socila and biological determinants of ill health (pSoBid) project in Glasgow. This interdisciplinary project conducted a research on the associations between an epigenetic marker and socio-economic status, the results of which were included in its final report aimed to inform and deliver policy action in Glasgow.

The research questions that this thesis asked include:

1) How is epigenetics mobilized and used in an interdisciplinary project that combines biological and social approach to health?

2) How do different actors conceptualize epigenetics within a collaborative health endeavour aimed to bring about policy and action upon health?

The methods used in this part of the research include qualitative reading of the literature published on the pSoBid cohorts and semi-structured interviews with experts from the pSoBid project, complemented by observational studies.

Interviews with professionals from the pSoBid project

Semi-structured interviews as method of data collection were selected as the most suitable for this part of the project because they provide ample space for professionals with different expertise involved in an interdisciplinary research project to express their views and opinions. Focus groups and survey research would be alternative methods to capture opinions and perspective of different actors but they require a much larger sample of people. Given the stage at which my project was at the time when the EPIGEN project was finalising its activities,

it was impractical, if not impossible, to gather numerous busy professionals in the same setting in order to organise focus groups. The initial idea to access health professionals at the EPIGEN International Conference could not be accomplished as they declined their invitations to come to Milan. Considering that this project was based in Italy, and that even the Italian epigenetic-epidemiologists are mostly based in the UK, reaching the conditions necessary for focus groups to take place on the UK soil would practically be impossible to accomplish. On the other hand, although open-ended questionnaires in survey methods provide a space for participants to express their opinions and experiences, the motives and meanings behind such responses cannot be explored as fully as they can be in semi-structured interviews. Semi-structured interviews were therefore selected as the most practical and effective way of collecting appropriate data for this part of the project.

Case study selection

While providing cartography of epigenetics in healthcare, the project also examined environmental epigenetics research, in particular, epidemiological studies on the health-related effects of environmental and social factors via epigenetics, such as:

a) Methylation status of IGF2 gene promoter in relation to nutritional factors in the Dutch Famine Birth Cohort Study (Heijmans et al 2008);
b) Methylation status of LINE-1/Alu sequences in relation to air pollution in the Boston area Normative Aging Study (Baccarelli et al 2009);

c) Methylation status of F2RL3 locus in relation to smoking in the European Prospective Investigation into Cancer and Nutrition (Shenker et al 2013);
d) Methylation status of various gene promoters in relation to socio-economic position (SEP) in the British 1958 Birth cohort (Borghol et al 2012);
e) Global methylation content in relation to socio-economic status (SES) in the pSoBid cohort (McGuinness et al 2012).

The last two studies, the McGuinness et al 2012 and Borghol et al 2012, study the same social factors – socio-economic status – and were published in the same special issue of the International Journal of Epidemiology that was dedicated to the prospects of epigenetics in and for epidemiology. A comparative analysis of the two studies was therefore performed to examine whether any of the two would be suitable for further analysis. The summary of this analysis that took place in April 2014 is presented in Table 7.

There were two main reasons behind choosing the McGuinness study for further exploration. First, the study was conducted on a cohort that was specifically designed for studying the effects of socio-economic circumstances on health (Velupillai et al 2008). On the other hand, the Borghol study was conducted on a birth cohort. Second, the McGuinness study was a policy-related study – it was initiated by the Glasgow Centre for Population Health to generate guidelines for health policy in Glasgow. The Borghol study was an explorative one. As this project was framed as 'epigenetics and policy', and sought to investigate how epigenetics is currently employed in research and action upon health, the McGuinness study was selected for further exploration as a case study of this thesis.

Study characteristics	Borghol et al 2012	McGuinness et al 2012
Social factor	Socio-economic position	Socio-economic status
Epigenetic data	Differential DNA methylation of promotors and enhancers	Global DNA methylation
Participants	40 out of 3362 eligible; men	239 out of 666 eligible; men and women
Cohort	1958 British Birth Cohort	pSoBid cohort
Purpose	Explorative	Policy-tied
Place	UK	Glasgow, Scotland
Media reports	No	Yes

Table 7: A comparative analysis of two International Journal of Epidemiology papers on the association between socio-economic circumstances and epigenetic differences (Borghol et al 2012 and McGuinness et al 2012)

Sampling

The interviews were conducted in October 2014 in Glasgow with support from external funding body – the COST Action IS1001 *Bio-objects and their boundaries: governing matters at the intersection of society, politics, and science*, under its Short Term Scientific Mission funding scheme. The allocated time for the fieldwork in Glasgow was one working week. Bogner, Littig and Menz, (eds. 20009) note three types of challenges in interviewing experts: sampling issues, the specific access problems and the challenges of conducting interview. The challenge of sampling and access to experts in this study arose due to shortness of the STSM in Glasgow, which could not be extended due to funding limitation. As a consequence, several of the pSoBid professionals were not available for interviews during the designated week in October 2014. Skype or phone

interviews were also difficult to organise due to their busy schedule. In order to conduct the STSM under the COST Action IS1001, a person from the University of Glasgow had to accept to host it. The initial contact was therefore established with the principal investigator of the McGuinness study via e-mail in which my interest in their work and the aim of my fieldwork of Glasgow was explained. The interviews were then scheduled with nine members of the pSoBid project, based on their availability during this STSM, while ensuring at the same time that the sample of people reflected the diversity of disciplinary expertise in the pSoBid. Assuring that the sample reflects the diversity of actors with respect to expertise they bring into the project was of particular importance considering the relatively small number of informants in this study. Four interviews were organised during a Skype call with the host of the STSM, while another four were arranged via e-mail.

A potential issue in receiving a positive answer by those pSoBid professionals that were already accessed appeared to have been the language. Namely, the informants confessed that the initial Skype calls were arranged to evaluate if my command of English is good enough, as they held some concerns about being interviewed by a non-native. Upon being assured that language will not be an obstacle in our conversations, they felt very willing and comfortable to enter into discussions and also engage with me informally during my stay in Glasgow. The issue of multi-lingualism in fieldwork is underexplored in literature, which usually assumes a monolingual research environment. Although this fieldwork was conducted in a monolingual manner, it is important to keep in mind that language-related challenges might arise when the interviews are to take place between non-native and native speakers, be it English or in any other language.

The interviews were scheduled with:

1) Head of the Laboratory on Biological Aging and Epigenetics, Institute of Cancer Sciences, University of Glasgow (member 1);
2) Head of the Healthy Working Lives Group, Institute of Health & Wellbeing, Public Health, University of Glasgow (member 2);
3) Research Associate in the Healthy Working Lives Group working on the Biology of the Workless, Institute of Health & Wellbeing, Public Health (member 3);
4) Research Associate in the Scottish Observatory for Work and Health, Institute of Health & Wellbeing, Public Health, University of Glasgow (member 4);
5) Head of the Health Economics and Health Technology Assessment, Institute of Health & Wellbeing, University of Glasgow (member 5);
6) Programme Manager in Public Health, Glasgow Centre for Population Health (member 6);
7) Programme Leader in Neighbourhoods and Health, and Social and Spatial Patterning of Health, Medical Research Council, University of Glasgow (member 7);
8) Clinical Lecturer in Public Health, University of Glasgow (member 8). All interviewees waived anonymity.
9) Professor of Global Health and former Chief Medical Officer for Scotland

Unfortunately, the interview with the last informant had to be cancelled due to this informant's unanticipated commitments. The final sample consisted of eight pSoBid professionals. Six interviews lasted for approximately one hour, while

two lasted for about ninety minutes. In addition, informal engagement and discussion took place with 3 of the informants on several occasions during my stay in Glasgow.

Interview Guide

Preparatory research for the fieldwork in Glasgow included a review of all publications produced on the pSoBid cohort; and activities and projects of the Glasgow Centre for Population health who initiated it; as well as getting familiarised with other work of the professionals involved in the pSoBid project that will be interviewed. These data were then used in building the interview guide. King and Horrocks' *Interviews in Qualitative Research* (2010) was consulted for designing the interviews guide and for conducting data analysis. This book provides clear and easy guidance on how to conduct interviews and it is an excellent resource for a novice in this type of research. Based on the preparatory research, two main themes were interrogated by these interviews: 1) the cooperation between professionals from different groups and of different background; and 2) the evidential value of epigenetic data in population studies and public health policy.

Several additional questions within these two broad themes were also examined:

- How did the actors come to collaborate in the first place? The DNA methylation analysis was conducted by a research group at the Institute for Cancer, which has no formal affiliation with the GCPH who initiated the pSoBid project. It is, however, through the University of Glasgow that the members of the pSoBid are formally connected, as shown in Chapter Five – Behind the 'Glasgow Effect'.

- How do actors of different professional/disciplinary background understand, interpret, value and utilise epigenetic evidence; do these and to what extent diverge among or have shared meaning between the actors?

- What is the perceived status of epigenetic evidence in public health compared to other (non-molecular) types of evidence, i.e. data coming from social epidemiology; and how is molecular evidence valued, in comparison with evidence of non-molecular kind; and incorporated with evidence of non-molecular kind?

- To what extent is epigenetics through to influence the ways in which public health research is conducted and policy strategies are devised?

- How is *in utero*/early childhood environment justified, evidentially, as a source of adult stage epigenetic differences (methylation levels), which were correlated with SES differences? The discussion part of the McGuinness study (McGuinness et al 2012) proposed that the effects experienced *in utero* and/or in early childhood could be a possible explanation for the results they observed. In addition, such explanation was picked up by the media, who publicized the study findings with the headlines like "Babies born into poverty are damaged forever before birth" (The Scotsman 2012[29]) and leads like "New research into DNA has shown that the health of deprived Glaswegians could be impaired before they are even born" (BBC News 2012[30]).

The questions that were used as probes within these two broad themes include:

- How did you get involved in the project? Can you tell me how the collaboration between you and other members started?

[29] Available at: http://www.scotsman.com/news/babies-born-into-poverty-are-damaged-forever-before-birth-1-2072713

[30] Available at: http://www.bbc.com/news/uk-scotland-glasgow-west-16680730

- How do understand the work and results of other people with different professional background; how do you talk with each other about it; can you tell me about any difficulties you might have experienced in that?
- Do you engage also with the public in Glasgow; can you tell me how?
- What do you think about epigenetics and molecular data? Why do you think the project collected also epigenetic data; do you think this was important? And what about other data, is this something entirely new and/or more important?
- How relevant, if at all, do you think *in utero*/early childhood environment is for health later in life?

The challenges in conducting interview can be in either over encouraging the interviewee to structure an account of the situation; or to allow the interviewee to introduce to a considerable account his own notion of what they regard as relevant instead of what the investigators regards as relevant (Dexter 2006/1969, p.18; cf. Bogner, Littig and Menz, eds. 2009). Bogner, Littig and Menz, (eds. 2009) thus suggest investigators to be extremely flexible while at the same time ensuring to present themselves as competent partners. My position as a junior researcher did not seem to pose an additional challenge in conducting interviews with the pSoBid professionals because my background in science made all the informants assured of my 'general competence'. The interviewees did not perceive me as 'inexperienced' but rather as 'a fellow expert in molecular biology' or 'an expert in a desirable area' (that is to say, molecular biology). Beside the possible challenge that my status of a non-native speaker could have had on the sampling procedure, the local dialect of Glasgow was at first one of my concerns in preparing for these interviews, particularly because audio

recording was not used (see below in the *Ethics approvals, risk consideration and reflexivity* section). However, this did not pose an issue in this study as all informants use formal English and not the local dialect. Besides my educational background, the willingness on the side of the interviewees to discuss openly and freely about their work relied, according to their own admission, on another rather surprising factor – my nationality, i.e. my social/communal background. I was thus perceived as a 'like-minded' person who can understand and appreciate what the community is about and what 'they are trying to achieve' by projects like the pSoBid.

Interview setting and rapport

All interviews took place in the offices of the informants. These included the Glasgow Centre for Population Health office, Institute for Cancer Sciences lab and office, Medical Research Council office, and Glasgow Public Health Institute of Health and Wellbeing where several of the informants hold offices.

At the beginning of each interview, I would introduce myself and my project, and briefly explain why I am interested in their project and work; as well as what I am interested to hear about from them in that interview: 1) how they started the whole project; why; and how do they collaborate and 2) what do they think about the use of epigenetics in their projects, and epidemiological projects in general, and why they think, if at all, it is important in such projects. The rest was then left to unfold during the interview, with occasional use of probes to stir the discussion. Since the interviewees waived anonymity, they were asked after the

interview if they considered anything that was being said as confidential and not suitable for later publishing. They were also told they will receive a report, which had to be submitted to the funding body of this STSM, that was produced upon the analysis of the data collected through these interviews.

Observational component

The original design of the STSM in Glasgow did not allow for participants observation or ethnography, as these would entail the extended involvement in the social life of the pSoBid professionals (Bryman 2012) while the STSM could last only for a week. However, informal engagement with several pSoBid professionals provided critical insights into informants' understanding of their role as both professionals and members of the community, and what the communal, local bonds and identity mean to Glaswegians.

The observational component entailed:

1) Attendance at a football match in Glasgow between Celtic FC and Saint Partick Thisle FC, which included the 'traditional walk' to the Celtic Park Stadium with Celtic fans through the deprived areas of Glasgow
2) Participating to post-match activities with Celtic fans in one of the traditional Celtic FC pubs in Glasgow
3) Attendance at a football match in Milan between Internazionale FC and Celtic FC in the knock-out phase of the Europa League, in the visitors' box with Celtic fans

4) Participating to pre-match activities with Celtic fans in Milan for two days, including city walks and pub hopping; as well as to post-match activities with Celtic fans, which included more pub hopping

Data analysis

Since audio recording could not be used in these interviews due to bureaucratic impracticalities related to ethics approval (see below), the elaborate and exhaustive notes were taken in each interview. The interviewees themselves did not feel disturbed by my taking notes. My years-long experience in taking notes in conversations with people in various settings I gained at my previous job proved a valuable asset in this setting. King and Horrocks' guide for qualitative researchers was consulted on how to get the best possible interview data by taking notes (King and Horrocks 2010). The notes were transcribed and converted into electronic format by myself after each interview, while additional comments and observations were also noted into the transcribed text.

Data analysis took the form of thematic analysis whereby the focus was on the two themes set before the interviews – collaboration between actors and the value of epigenetic data in research and policy – and what views, opinions perspectives were elicited by in-depth discussion. Because of the small number of informants who at the same time waived anonymity, the analysis also focused on to what extent and how does disciplinary and/or professional background influence perceptions about epigenetic data; does junior/senior level within the project play a role and how; how informants spoke about other informants and their work; and how informants perceived their own role in their discipline,

within the project and in future projects. Another theme emerged from the data – communal identity and membership. This concept first emerged during the interviews but it was only after observational component was included into the data that the communal identity and membership emerged as a theme that cuts across all the others. A preliminary analysis of the data had to be completed within four weeks after the STSM and shaped into a report, as the external funding body required such a report for the final approval of this work. This report was also sent to all the interviewees.

Observational studies were conducted through informal engagement with pSoBid researchers, which unintentionally included engagement with also pSoBid participants. This took the form of attending football matches and engaging in football supporting activities of the Celtic Football Club (FC) in Glasgow, during the STSM, and later in Milan. The observational data on football-related activities were included into data analysis as they provided not only additional source of information that helped identify the communal identity and membership as a third theme, but the only possible way of gauging the meaning of this theme for the professionals involved in the pSoBid project.

Ethics approvals, risk considerations and reflexivity

Obtaining ethical approval for this study from home institutions – the European Institute of Oncology (IEO) and the University of Milan (UoM) – was neither required nor was it possible. These institutions only processed application regarding their own personnel (IEO) or for the studies conducted in Italy

(UoM)[31]. The issue therefore was whether ethics approvals should be sought from the host institution – the University of Glasgow (UoG), and all other institutions with which the informants are affiliated – Institute of Cancer Sciences, Glasgow Centre for Population Health, Institute of Health and Wellbeing and Medical Research Council. Such process would be long and cumbersome, while the time of the fieldwork could not have been moved due to the external funding body limitations – the fieldwork could have only been approved in August 2014, while it had to be completed by December 2014. As a solution for these conflicting requirements, an agreement was reached with my STSM host and other informants whereby they would waive anonymity but that audio recording would not be used during these interviews. This study exemplifies how plurality of regulatory frameworks and procedures with respect to approvals can appear as a potential source of difficulties for trans-national and multi-cultural fieldwork. These difficulties have to be tackled and managed on a case-by-case basis, and this requires a lot of flexibility not just on the side of the researcher but also on the side of the prospective informants.

The data collected for the first aim of this project come from published and/or publicly available sources and hence raises no ethical concerns. The data collected through interviews were obtained with the consent from all informants. The informants' role as group leaders/representatives were disclosed, but none of the informants were named in any public presentation of

[31] In July 2015, the University of Milan Ethics Committee extended its competencies to studies taking place outside of Italy and now considers such applications for research outside of Italy. This change is a result of joint work by myself, Luca Marelli and Giuseppe Testa

the data. In addition, the results of how the data collected through interviews and observational study were used in my thesis were presented to each of the informant in the form of a written report. All informants expressed no concerns or complaint over how their work, views and perspectives were presented in the report. The observational study data pose no ethical concerns or risk either, as all the participants remained known only to the extent that they are Celtic FC supporters.

This research was eventually approached from an interpretivist position whereby multiple versions of reality are possible. However, the philosophical assumptions that underlie this research are those of critical empiricism, as found in King and Horrocks:

> »Behaviour and experiences are seen to be 'generated by' underlying structures such as biological, economic or social structures». (King and Horrocks 2010, p. 9):

Accordingly, the methodological approach employed is that of contextualism rather than of full-blown constructivism. Given the original structuring of this research through the objectives set up by the EPIGEN project, the only possible methodological approach in this project was that of methodological pragmatism (Tashakkori and Teddlie 2010, eds.).

Besides empirical reflexivity, Willig (2001) distinguishes also personal reflexivity, whereby contingencies of our experiences and life influence the process of research in all its stages (Willig 2001). In this respect, my previous

involvement with non-governmental organisation where I worked with vulnerable groups of people living in or coming from the conditions of extreme poverty might have played a contributing factor in choosing to focus on health inequalities rather than on innovation practices in biotechnology. Accordingly, the aspirations and deontological claims to remedy to the long-suffered injustices of Glaswegian community expressed by my interviewees resonated with my own aspirations and expectations of what science should be about and for. The project's exploration of solidarity also reflects my own interest in solidary practices. I believe, however, that these considerations worked to the project's best interest and not against it.

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CHAPTER FOUR – BEYOND THE GENOME

INTRODUCTION

This chapter presents empirical data gathered through combined qualitative-quantitative strategy developed within this project to present the most active areas of epigenetic research, clinical application and clinical outputs. It also presents data on how 'environment' is conceptualised/addressed in epigenomic practice; and on environmental epigenetics research and its commercial application. The chapter finds that the most actvevly studied diseases in epigenetic research reflect the diseases reported by the WHO as major contributors to the burden of disease in both 'developed' and 'developing' countries and regions of the world. The chapter also finds that epigenetics goes 'beyond the genome' insofar as what lies beyond can be converted into genome-friendly, code-compatible manner that is to say into digital representations (Meloni and Testa 2014).

THE IMPACT OF EPIGENETICS ON HEALTH CARE

The methods used in this part of the research project include systematic review and qualitative reading of biomedical literature gathered through PubMed database; systematic review and qualitative analysis of cancer clinical trials gathered through the National Cancer Institute (NCI) and the European Union Clinical Trial (EU-CT) registers. The analysis took the form of compiling lists of

the results in Microsoft Excel files and visualising the data using Microsoft Excel tools.

The search terms used to capture translational and clinical research were 'epigenetics, treatment' and 'epigenetics, treatment, clinical trial' respectively. Additional key words were used in combination with each of these search terms to determine the most actively studied disease areas included: cancer; cardiovascular diseases; neurodegenerative diseases; autoimmune diseases; type 2 diabetes. The results of these searches are shown in Figure 1.

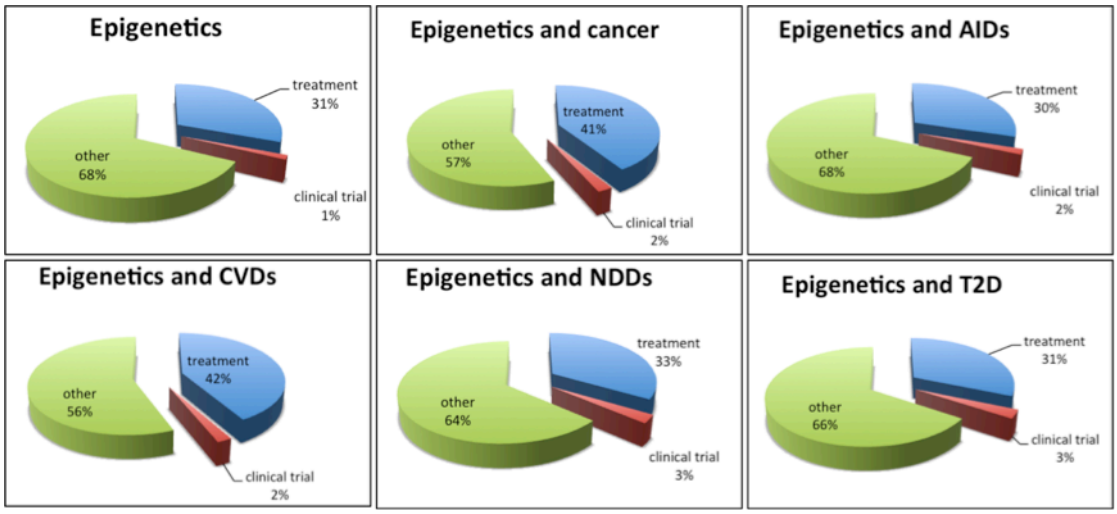

Figure 1 - Types of research within the field of epigenetics.

Source: PubMed 2014

The 'treatment' part of the pie in Figure 1 represents translational research; 'clinical trial' part represents clinical research; while 'other' section of the pie represents 'basic research'. The 'basic research' section was calculated by subtracting the results on 'translational research' and clinical research' from the results of 'total epigenetics', i.e. it is represented by the part of all epigenetic

research that is neither translational nor clinical. Basic research was identified as the most active type of research within the field of epigenetics in general (68%, the top left graph of Figure 1), as well as in epigenetic studies of the five selected disease areas (other graphs in Figure 1). A significantly smaller size of the area representing clinical research (1-3%) is expected to occur in all biomedical sciences, not just the emerging ones like epigenetics. This should especially be kept in mind in light of the results of how much is translational research represented within all epigenetics research – between 30% and 40%.

The search terms used in identifying the most actively studied diseases were selected upon general review and qualitative reading of biomedical literature on epigenetic research. Figure 2 show results of the searches related to identifying the most actively studied disease areas in basic, translational and clinical epigenetic research.

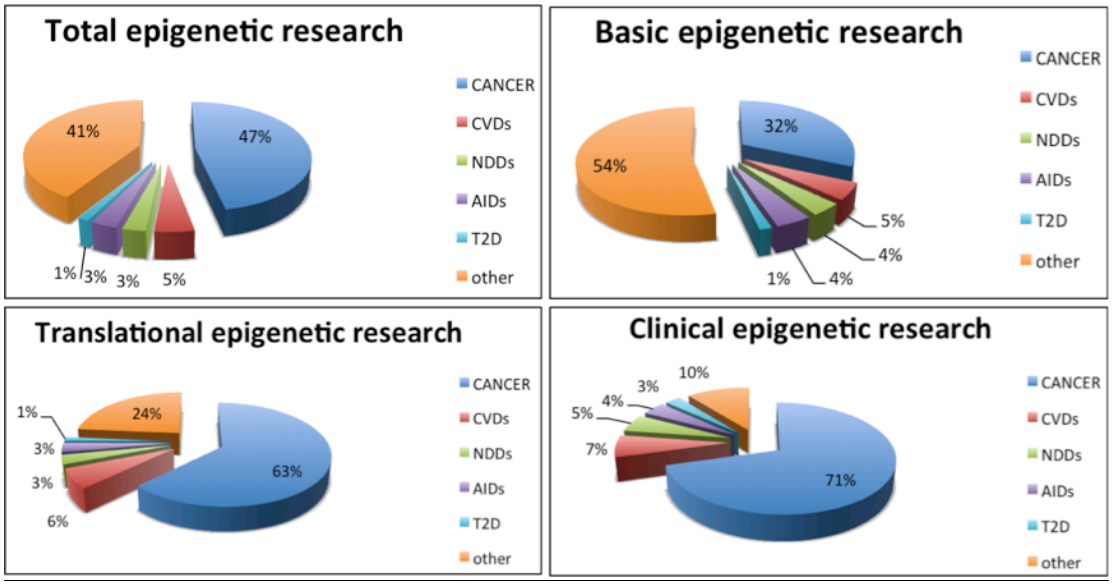

Figure 2 - The most actively studied disease areas in epigenetic research.

Source: PubMed 2014

Cancer was identified as the most actively studied disease area within the field of epigenetics in general (47%, the top left graph in Figure 2), as well as in all types of epigenetic research (other graphs in Figure 2). In clinical research in particular, cancer dominated the results with the score of 71% (the bottom right graph in Figure 2). These diseases were reported by the WHO, with the exception of autoimmune diseases, as the major contributors to burden of disease in both 'developed' and 'developing' countries and regions of the world (WHO 2008). Moreover, cancer, neurodegenerative diseases and autoimmune diseases are the diseases studied within the NIH Roadmap Epigenomics project (Epigenomics Roadmap Project 2015).

The thirty one papers obtained in a search that used 'epigenetics, treatment, clinical trial, cancer' as search terms were submitted to qualitative reading to identify which epigenome-modifying mechanisms are the most studied ones in clinical research. The results of this study are shown in Table 3 in Chapter Three – Research Design and Methods. The following searches conducted in the databases on clinical trials did not yield any results when 'epigenetics' was used as the key word. More fine-grained terms were therefore necessary in order to conduct such studies. Cancer as a case study was, on the other hand, selected because it scored the highest in all the performed searches, reaching 71% in the clinical research (Figure 2, the bottom right graph). The results of the qualitative reading of cancer clinical research are shown in Figure 3. The most actively studied targets in epigenetic therapies in cancer are DNA methyltrasnferases

(DNMT) and histone deacetylases (HDAC), or a combination of both (DNMT and HDAC). Section 'other' in Figure 3 represents uncategorised targets.

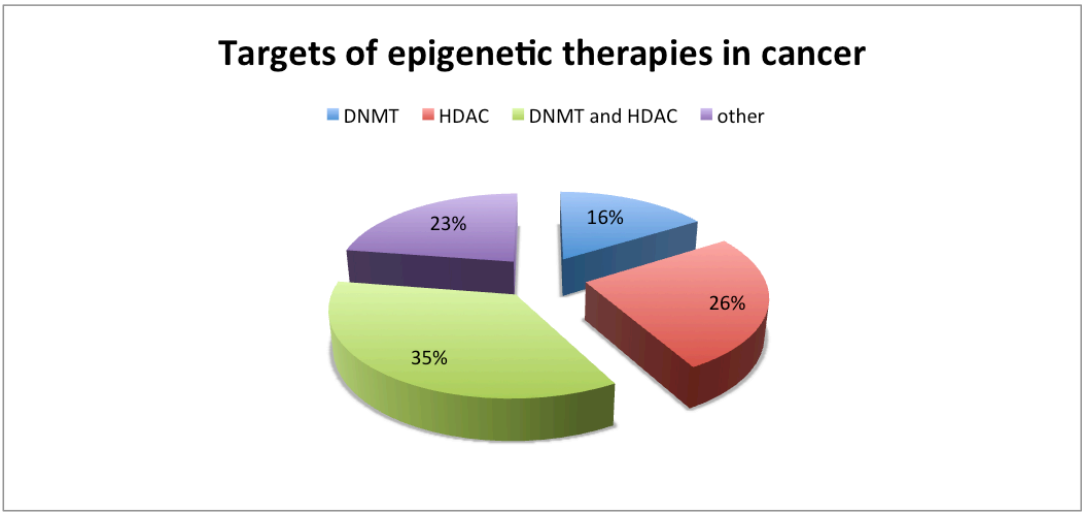

Figure 3 - Targets of epigenetic therapies in cancer. Source: PubMed 2014

These results therefore formulated search terms for a study on clinical applications of epigenetics. A study about on-going clinical trials at the National Cancer Institute (NCI)[32] was conducted to examine the types of cancer care (treatment, prevention, diagnosis, etc.) for which the targets of epigenetic therapy are currently in clinical testing. The results for histone deacetylases and methyltranspherases are shown in Tables 8 and 9 respectively in Chapter Two – Methods.

These clinical trials reported in the results of these searches were subjected to qualitative analysis to confirm that the compounds they test for do, indeed,

[32] Available at http://www.cancer.gov/clinicaltrials (Last accessed on 12.12.2016.)

target the epigenome. Treatment and biomarker/laboratory analysis[33] are the dominant areas of cancer care for both HDAC inhibitors (HDACi) and DNMT inhibitors (DNMTi), but several trials are conducted in the areas of supportive care and diagnosis, as well as prevention. According to the results obtained through NCI database, thirty-six epigenome-modifying compounds are currently tested in cancer, and most of them target histone deacetylation. Most of these epigenome-modifying compounds are in the first two phases of clinical testing Figure 4), which are conducted for testing the safety of a drug and not for its efficacy in treatment

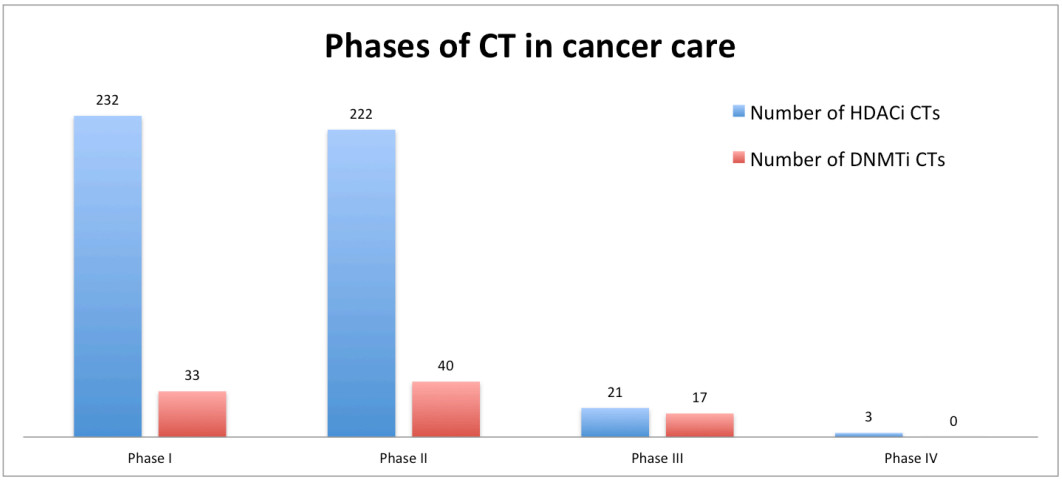

Figure 4 - The phases of clinical trials of currently tested epigenome-modifying compounds in cancer.
Source: NCI 2014

The epigenome-modifying compounds that are currently tested in five of more clinical trials (CTs) are shown in Table 8.

[33] The NCI database has embedded, non-modifiable categories within search criteria. Biomarker/laboratory analysis category is in most cases combined with treatment category as a 'type of trial'

	Generic name	No of CTs
1	Vorinostat	123
2	Panobinostat	89
3	Romidepsin	39
4	Temozolomide	28
5	Valproate	27
6	Belinostat	18
7	Entinostat	17
8	HDACi general	12
9	Decitabine	9
10	SGI-110	8
11	DNMTi general	6
12	Ricolinostat	5
13	Pracinostat	5
14	Azacitidine	5

Table 8: The most actively tested epigenome modifying compounds in cancer clinical trials. Source: NCI 2014

The search on epigenome-modifying compounds that target histone deacetylases and DNA methyltranspherases was then conducted using also the EU clinical trial register (EU-CTR) database. The results of this search are shown in Table 9.

	Generic name	No of CTs
1	Temozolomide	115
2	Azacitidine	53
3	Valproate	39
4	Mercaptopurine	38
5	Decitabine	25
6	Panobinostat	22
7	Vorinostat	17
8	Romidepsin	7
9	Belinostat	6
10	Givinostat	6

Table 9: The most actively tested epigenome modifying compounds. Source: EU-CTR

The compounds identified in these studies were then searched for in the US Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) databases to check which of them, if any, have previously received market authorisation; under which market name; and for what condition. The list of epigenome-modifying compounds that are received market authorisation until August 2014 is shown in Table 10. The FDA authorised nine such epidrugs, while the EMA authorised five were. In addition, Panobinostat and Tecadinaline are two HDAC inhibitors that are in phase three of clinical testing, which aims to demonstrate the drug's efficacy in disease treatment. Moreover, a companies that offer a range of *in vitro* tests for several epigenetic markers in cancer treatment, e.g. Oncomethylome Sciences, Epigenomics AG, Sequenom, Exact Sciences are emerging; and one such test received market authorisation from the FDA in 2014 (a combined four methylation markers test for early detection of colon cancers by the Exact Sciences company).

Most of these drugs have reached the market in the last 10 years, but several received market authorisation before the year 2000, i.e. prior to the beginning of the 'exponential rise' in publications on epigenetics (Haig 2012; Jirtle 2012). One such drug is on the market since as early as 1953, when the FDA approved market authorisation request to the TEVA Pharmaceutical Private Limited Company for Purinethol. As it happens in general with drug approval applications filed for different markets, which operate in different regulatory frameworks, an epigenome-modifying compound Istodax (romidepsin) of the Celgene Europe Ltd. Company received market authorisation by the US Food and

Drug Administration in 2009, while the European Medicines Agency rejected their application twice in 2012[34].

Generic name	App	Condition*	Market name
Valproate	FDA	anticonvulsion	Depakote-ER-CR/Depakene/Stavzor/Depacon
Vorinostat/SAHA	FDA	CTCL	Zolinza
Romidepsin	FDA	CTCL, PTCL	Istodax
Belinostat	FDA	PTCL	BELEODAQ
Sodium phenylbutyrate	FDA EMA	UCD	Buphenyl/SODIUM PHENYLBUTYRATE/Ammonapse/Pheburane
Temozolomide	FDA EMA	GBM	Temodar/Temodal/Temomedac/Temozolomide-Hexal/Hospira-Sandoz-Sun-Teva
Mercaptopurine	FDA EMA	ALL	MERCAPTOPURINE/PURINETHOL/PURIXAN /Xaluprine
Decitabine	FDA EMA	MDS/AML	Dacogen/Decitabine
5-azacytidine	FDA EMA	MDS	Vidaza/Azacitidine

Table 10: The list of epigenome-modifying compounds (epidrugs) currently approved by FDA and/or EMA.

Source: FDA 2014; EMA 2014; NCI 2014; EU-CTR 2014

***CTCL – cutaneous T-cell lymphoma; PTCL – peripheral T-cell lymphoma; UCD – urea cycle disorder; GBM – glioblastoma; ALL – acute lymphoblastic leukemia; AML – acute myeloidic leukemia; MDS – myelodysplastic syndromes**

[34] Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002122/smops/Negative/human_smop_000407.jsp&mid=WC0b01ac058001d127 (Last accessed on 12.12.2016.)

THE 'ENVIRONMENT' IN EPIGENOMIC SCIENCE

With the advent and rapid development of sequencing-based technologies, much of today's science of epigenetics is concerned with producing genome-wide maps of various DNA and chromatin modification, as well as chromatin structures across the whole genome. This science of genome-wide mapping of epigenetic modifications goes by the name 'epigenomics'. In the last couple of years, many national and supranational epigenomic projects and/or consortia were initiated with the aim of producing high-resolution reference epigenomes for different cell types. Results of one such project, the NIH Roadmap Epigenomics project, were collectively published in a special issue of the journal *Nature* in February 2015 (Nature 2015). The NIH Roadmap Epigenomic project was initiated in 2010 and consisted of five research initiatives. One such initiative was on human health and disease, which supported also the research on responses to exposures such as physical, chemical, behavioral, and social factors[35]. The eight threads in which its Nature papers were published include: annotation of the non-coding genome; relationship between different epigenomic marks; epigenomic changes during differentiation and development; regulatory models: networks, motifs, modules, sequence drivers and predictive models; interpreting variation: GWAS, cancer, genotype, evolution and allelic; epigenomic changes in human diseases and during cancer progression; brain epigenomics; and computational tools and methods. None of the twenty-one publications produced by the project was concerned with *responses* to environmental factors. Only one paper mentioned environmental exposures and it did so in its introduction - *Sexual dimorphism in*

[35] Form more information see http://www.roadmapepigenomics.org/overview/epigenomics-human-health (Last accessed on 12.12.2016.)

epigenomic responses of stem cells to extreme fetal growth (Delahaye *et al*. 2015). One paper mentions the environment as something to control against (Lowdon *et al*. 2015). Another paper mentions it in the discussion part as a side-note of how the results presented relate to the general picture of the Alzheimer disease model (Gjoneska *et al*. 2015). Other papers that do contain just the word 'environment', the word is found in the references or in the acknowledgments. The reference in almost all cases being the *Genome-wide chromatin state transitions associated with developmental and environmental cues* by Zhu *et al*. 2015. The acknowledgment was always the same and referred to the National Institute of Environmental Health Sciences. In most of these papers the words 'environment' and 'environmental' are entirely absent. The papers, however, employ all the expressions from genomic vocabulary, e.g. functional annotations, datasets, regulatory networks, mapping, etc. The lack (or complete absence) of 'environment-related discourse and, correspondingly, the dominance of 'genomic' (or '-omic' in general) discourse suggest that the environment in epigenomic science and practice is being taken into consideration insofar as it could be represented in a 'genome-friendly, code-compatible', that is to say, digital manner (Maloni and Testa 2014).

At the same time, in the big and growing field of epigenetics a small corner *is* concerned with molecular relationship between factors such as chemicals, smoking, diet, exercise, etc., and health-related conditions like elevated blood pressure, anxiety, obesity, etc. in a *causal, mechanistic* manner (Landecker and Panofsky 2013). Factors like child neglect (i.e. parental care, Weaver et al. 2004), poverty (i.e. socio-economic circumstances, McGuinness et al. 2012; Borghol et

al. 2012) or substance abuse (i.e. drug addiction, Renthal and Nestler 2008), are the subject of study for a few of them. The pioneering experiments in this area have been produced by an interdisciplinary team of scientists at the McGill University in Montreal. A study conducted on a rat model of maternal care showed that having attentive or inattentive mothers caused differences in the methylation status of two genes in the brain of the pups: 1) the glucocorticoid receptor gene, which has a role in stress responses, and 2) the oestrogen receptor gene, which has a role in parental behaviour. The study was published in the journal *Nature Neuroscience* under the title *Epigenetic programming by maternal behaviour* (Weaver et al 2004). This study has paved the way for the establishment of research fields that connect epigenetics to the research programmes of other disciplines such as environmental epigenetics, behavioural epigenetics, social epigenetics and nutritional epigenetics. However, the results of such studies and the scientists that conduct them are received rather critically and with a high dose of skepticism within the wider field (Pickersgill 2016). My own experience of four years of working in a research institution, which required doing bench work for a year, attending two lab meetings and one seminar per week, presenting scientific publications of this kind (e.g. Padmanabhan et al 2013) at journal clubs, and presenting my own data to the lab and Institute colleagues as well as at the annual meetings of the EPIGEN consortium, confirms such general attitude of suspicion and cynicism among fellow epigeneticists regarding environmental epigenetics research and results. Despite representing such small corner of the field, or perhaps because of it, these studies gain the most attention outside of the field, including in social studies of science. Accordingly, several companies that seek to provide their

products and services with scientific legitimacy have recognized its commercial potential, which is discussed in the following section.

COMMERCIAL APPLICATION OF EPIGENETICS IN NON-MEDICAL SECTORS

Drawing on results of experiments with agouti mice, which demonstrated that diet is responsible for phenotypic differences (Waterland and Jirtle 2013) and studies in humans that suggest that diet of parents affects growth and metabolism in children (Tobi et al. 2014), nutrition industry has endorsed epigenetics in its science-based justifications of their products' health benefits. For example, Reliv International Company released 'the epigenetic superfood' product called LunaRich[36]. This product is based on a naturally occurring soy peptide called lunasin, for which the company claims to be 'the first dietary ingredient identified to affect gene expression and promote optimal health at the epigenetic level'. According the LunaRich advert, lunasin is one of the most heavily researched and scientifically supported nutritional compounds available today, with over 30 research institutions, 20 funding sources, and 80 published papers behind it. The adverts go on to explain what epigenetics and epigenome is, emphasizing that 'while you can't change your DNA blueprint, you can influence the way that DNA expresses itself.' Considering its numerous health benefits – cholesterol management, inflammation reduction, antioxidant benefits, improved immunity, and cellular health – the take-home message directed at prospective customers is that "with lunasin, you really can take

[36] Available at: https://reliv.com/lunarich (Last accessed on 12.12.2016.)

control of your health».[37] Other companies have gone even further and endorsed epigenetics as their future investment. Nestlé, one of the most valuable companies in the world (Forbes reports Nestlé as 33rd on its World's Biggest Public Companies list, with an estimated worth value of $235.7 billion[38] US dollars – over 30 billion more that the biggest pharmaceutical companies like Pfizer and Novartis) recently announced that they would contribute 22 million Swiss Franks to a six-year research project into maternal nutrition and epigenetics – 'the science of how eating behaviours and other environmental factors can affect your genes, health and that of your offspring, for future generations to come'. At the time when this company is fighting allegations using of child labour in Ivory Coast farms[39], Nestlé has announced a partnership with an international alliance of researchers at institutions in Southampton, Auckland and Singapore, who make up the EpiGen Consortium, and that being involved in 'such cutting-edge research in such a vital and exciting field' will enable the company to "create products that have a proven, positive impact on the health of mothers and their children. Ultimately, being a leading Nutrition, Health and Wellness company is about improving the quality of peoples' lives"[40].

In a similar fashion, epigenetics has landed itself a top spot on the long list of science-based approaches to cosmetics and the marketing of its products. For example, a journal called *Cosmetics & Toiletries: Science Applied* published an

[37] Available at: https://reliv.com/lunasin-and-epigenetics (Last accessed on 12.12.2016.)
[38] Available at: http://www.forbes.com/companies/nestle/ (Last accessed on 12.12.2016.)
[39] Available at: https://www.theguardian.com/global-development-professionals-network/2015/sep/02/child-labour-on-nestle-farms-chocolate-giants-problems-continue (Last accessed on 12.12.2016.)
[40] Available at: http://www.nestle.com/media/newsandfeatures/nestle-research-epigenetics (Last accessed on 12.12.2016.)

article *Epigenetics and Aging: A New Player in Skin Care*[41], with references to many papers published in prominent scientific journals, like PLoS Genetics (Gronniger et al. 2010), Cell (Rando and Chang 2012) and Nature Genetics (Wang et al. 2008). Accordingly, several cosmetic companies have marketed, or announced intentions to market 'epigenetics-inspired' products. An example of such a product is Re-Nutrive Ultimate Lift Age-correcting creme by Estée Lauder, a discovery inspired by the field of epigenetics. The Estée Lauder's advert for Australian market stated that its company's is further advancing its 'decades of scientific expertise and innovation', to help you repair, recharge and restore your skin's energized, radiant appearance[42]. Other examples of epigenetics as a 'new paradigm' in whatever the companies' business is about, include also healing and other forms of alternative medicine. Epigenetics Healing Centre offers services of functional medicine, hyperbarics, nutritional counseling, and prenatal care.[43] Another company, which claimed to have been a 'proud supporter of Team GB' at the 2016 Olympic Games, offers various products and services, all in this way or another related to or with epigenetics - hence the company's name, Epigenetics Limited.[44]

In recent years, the epigenetic effects of meditation have not only been investigated but some studies have, in fact, been published (Kaliman et al. 2013).

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[41] Available at: N.K. Konstantinov, C.J. Ulff-Møller, S. Dimitrov and H.I. Maibach, Epigenetics and Aging: A New Player in Skin Care, Cosm & Toil 130(9) 32-37 (Nov/Dec 2015) - See more at: http://www.cosmeticsandtoiletries.com/research/biology/Epigenetics-and-Aging-A-New-Player-in-Skin-Care-352273491.html#sthash.o5n5VJNc.dpuf (Last accessed on 12.12.2016.)

[42] Available at: http://www.esteelauder.co.th/media/boutiques/re-nutriv/2/life-re-newing-molecules.html#!/re-nutriv/1 (Last accessed on 12.12.2016.)

[43] Available at: http://drgoodbinder.com/services/ (Last accessed on 12.12.2016.)

[44] Available at: http://www.epigenetics-international.com (Last accessed on 12.12.2016.)

But in some cases, epigenetics healing has been taken to mean that no treatment is necessary as we can heal ourselves and now epigenetics proves it, as it (finally) 'explains how energy healing techniques work'. In reviewing follow-up stories of the 2010 Time magazine cover that appeared on various media channels, the search results led to a webpages discussing a popular book called *The Genie in Your Genes: Epigenetic Medicine and the New Biology of Intention* (Church 2007). This book contains references to many epigenetic studies but upon describing them, the text would subtly slide into a different interpretation of the results of these studies, presenting them as explanations of the mechanisms by which meditation and positive thoughts operate, as well as confirmations of holistic and energy healing. By April 2014, this book received 81 comments on Amazon and the overall rating of 4.5 stars. For a comparison, 'non-alternative-healing' books on epigenetics received two or three, at the best. Of those 81 people commenting on the book, only one former researcher and teacher at the time, and one doctor-gynecologist, bothered to object to the overwhelmingly positive reviews. They did so, according to their own admission, because they had to face a student and a patient who refused medical treatments after reading this book. The rest of the comments were overwhelmingly positive and welcoming of the new age ear of epigenetics, rating this book with the maximum of 5 stars in 64 out or 81 cases.

TRACKING THE NUMBER OF PUBLICATIONS ON EPIGENETICS

The purpose of a study to track the number of publications on epigenetics was to verify the claims that publications on epigenetics record an exponential increase

in the last decade (Haig 2012; Jirtle 2012). This was understood within the EPIGEN project as particularly important in order to provide a quantifiable report on every aspect of the 'expected impact of epigenetics on health care'. Data from two independent searches conducted for the period 2008-2013 confirm that there is, indeed, an increase in the number of publications on epigenetics in the specified period, as shown in Figure 5. However, the curve is far less steep than the one reported by Haig (2012) and the absolute number reached for every year is far below those anticipated by Jirtle (2012), which reached several thousands and were forecasted for up to 20,000 for the year 2011.

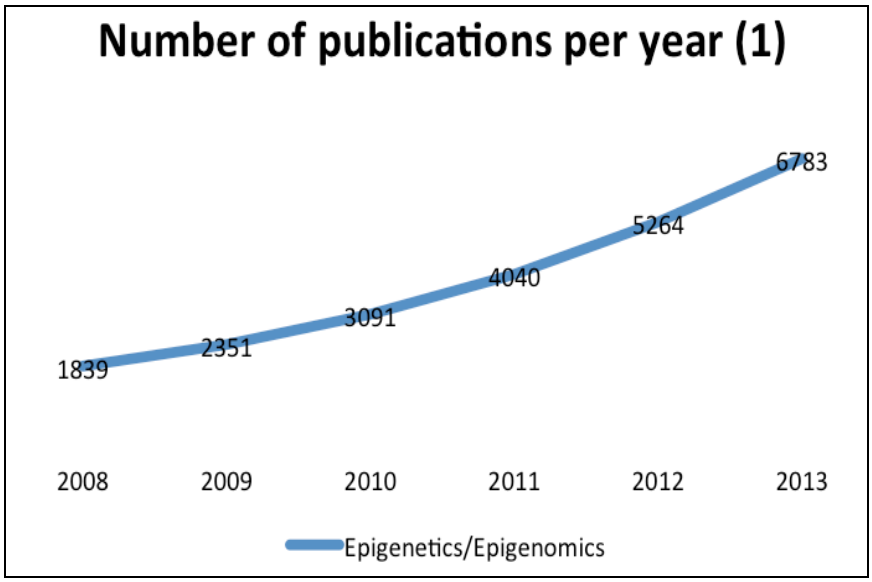

Figure 5 - The number of publications on epigenetics/epigenomics per year for the period 2008-2013

Source: webpages of the top biomedical journals according to ISI Web of Knowledge 5-year Impact Factor 2012

On the other hand, Figure 6 shows results of the second search, which was, instead, a small-scale comparative investigation into the number of publications on epigenetics and genetics. Since this search was aimed at probing if, in fact, the increase in the number of publications can be detected in the fields of both genetics and epigenetics, the search was done with less precision than the previous one. Instead of journal's webpages, PubMed was used as a source. The absolute numbers in the Figure 6 are therefore not representative of the actual numbers, but are not of not of great importance because the focus is on the relative ratio between the two fields. Interestingly, the genetics/genomics curve in the graph shows an even greater increase in the number of publication per year, i.e. it is steeper, than the epigenetic/epigenomic one.

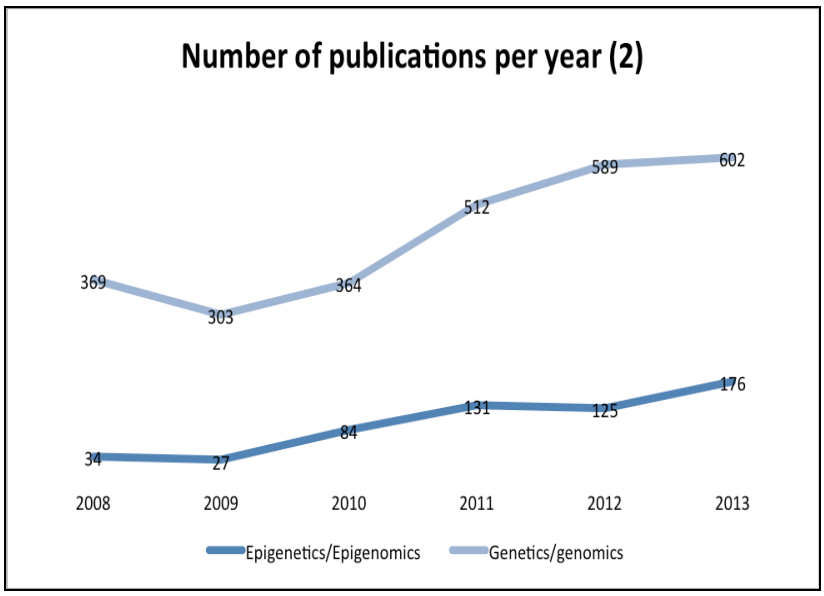

Figure 6 - The number of publications on genetics (top curve) and epigenetics (bottom curve) per year for the period 2008-2013. Source: PubMed 2013

These results suggest the increase in the number of publications on epigenetics is concurrent with the increase in the number of publications on genetics. Similar

case might be, and probably is, with other fields in the life sciences. The consortia-like projects are being established for other research fields beside epigenetics, such as proteomics[45], cancer[46], or immunology[47], to list a few. The same applies to the establishment of new scientific journals. Increase in the number of publication on epigenetics should thus only indicate that more scientific papers are being published as technological power increases and funds are flowing into science.

CONCLUSIONS

This research was initiated in order to map and measure the impact of epigenetics on health care. The results show that epigenetics is actively employed not only in basic research but also in translational and clinical research. Moreover, epigenetic research outputs like epigenome-modifying compounds already have clinical impact. Numerous drugs with epigenetic mechanism of action have already been used in treating diverse types of cancer – glioblastomas, leukemias, lymphomas, etc. Some drugs that have been authorised many decades have now been shown to have epigenetic mechanism of action such as TEVA's Purinethol. Accordingly, the disease areas that are most actively studied in epigenetic research, and where epigenetics is expected to make the greatest impact, are precisely those areas that the public health

[45] For example, Human Proteome Project, available at: http://www.thehpp.org (Last accessed on 12.12.2016.)
[46] For example, Cancer Stem Cell Consortium, available at: https://ccrod.cancer.gov/confluence/display/NCICSCC/Home (Last accessed on 12.12.2016.)
[47] For example, Human Immunology Project Consortium, available at: http://www.thehpp.org (Last accessed on 12.12.2016.)

agencies like the WHO and the political bodies like the EU identify as posing major challenges to the health of the population (WHO 2008; 20012; EC 2007). In addition, these diseases have long been known, or have been suspected, to be under the influence of factors other than genetics. In order words, factors that are not the DNA sequence itself – which could be considered a 'genomic paradigm' in the understanding of health – but by factors that are *beyond* the genome such as life styles related, environmental and social factors.

The big epigenetics consortia that have been established in recent years as follow up projects of Human Genome Project (HGP) and the Encyclopedia of the DNA elements project seem to affirm that beyond the genome *can* go all the way to the social and environmental factors. The International Human Epigenom Consortium (IHEC), for example, states that their long terms objective is to understand 'the extent to which the epigenome has shaped human populations over generations and in response to the environment'[48]. Similarly, the NIH Roadmap Epigenomics states that their *Epigenomics of Human Health and Disease Initiative* will support research on also response to exposures *such* as physical, chemical, behavioral, and social factors[49]. However, upon closer inspection, most of their published data do not even contain the word 'environment'. These publications, instead, employ all expressions from the genomic vocabulary, e.g. functional annotations, datasets, regulatory networks, mapping, etc. The lack (or complete absence) of 'environmental' discourse' and, correspondingly, the dominance of 'genomic' (or '-omic' in general) discourse suggest that the environment in epigenomics – the dominant practice of today's

[48] Form more information see http://ihec-epigenomes.org/about/objectives/ (Last accessed on 12.12.2016.)
[49] Form more information see http://www.roadmapepigenomics.org/overview/epigenomics-human-health (Last accessed on 12.12.2016.)

epigenetic science – is conceptualised insofar as it is and could be converted into genome-friendly and code-compatible digital representations (Maloni and Testa 2014).

On the other hand, a small corner of the field is concerned with the causal relationship between factors such as chemicals, smoking, diet, exercise, etc., and health-related conditions like elevated blood pressure, anxiety, obesity, and it goes by the name environmental epigenetics. Yet, the results of such studies are received rather critically and with a high dose of skepticism within the wider field (Pickersgill 2016). My own experience of working for four years in a research institution confirms such general attitude of suspicion and cynicism among fellow epigeneticists regarding environmental epigenetics research and scientists that conduct it. It is precisely such studies, on the other hand, that gain the most attention outside the field, in epidemiology, popular culture, humanities and social studies of science, as well as in non-medical commercial sectors.

Accordingly, the enthusiasm for epigenetics in the wider society has not only been recognized but also exploited by the very same epigeneticists who hold environmental epigenetic research and results to be suspicious (Pickersgill 2016). It has been previously shown that scientists tend to enthusiastically overstate the potential of their research field in order to create and meet expectation in related communities of practice, funding agencies and the wider public, and perpetuate dynamism and momentum (Brown and Michael 2003). In this respect, the expectations of epigenetics seems to operate o two levels: 1) epigenetics goes 'beyond the genome' but only insofar as it converts the environmental, the social, the biographical – into 'a genome-friendly and code-compatible (Meloni and Testa (2014); and 2) epigenetics shows how the

contingencies of life – what we eat, pollution or stress – affect how genes operate. In other words, how the environment, biography and milieu become molecularly embodied (Landecker 2011; Niewhoener 2011).

The discourse on genome-compatible digitization of what lies beyond the genome resonates better with the wider research community but has not been taken up beyond the life sciences. The discourse on molecularisation of the environment, on the other hand, has been marginalized within the research community but resonates well with wider society, including social inequalities in health paradigm. This research further focuses on one project on social inequalities of health in Glasgow, which investigated the association between socio-economic status and an epigenetic marker (among other factors), and group of people gathered around this project – the psychological, social and biological determinants of ill health in Glasgow (the pSoBid project).

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CHAPTER FIVE – BEHIND THE 'GLASGOW EFFECT'

INTRODUCTION

This chapter presents on empirical data collected through semi-structured interviews and observational studies to discuss how molecularisation of the environment (Landecker 2011; Niewhoener 2011) is employed in research and health policy. It discusses collaboration among actors of diverse background in the pSoBid study; epigenetic data as 'evidence' in research and policy action; and communal identity and membership as the driving engine behind the pSoBid collective endeavour. The chapter finds that it is thanks to its molecularization of the environment and therefore its purported objectivity, that epigenetics is bestowed the potential for actionable public health knowledge within the pSoBid project. In addition, the chapter also finds that it is the solidary practice that governs the interdisciplinary collaborative endeavour in Glasgow that is the pSoBid project.

BACKGROUND – 'EPIGENOMIC SIGNATURE OF POVERTY' IN GLASGOW

The McGuinness study, published in the International Journal of Epidemiology, reported that socioeconomic status (SES) is associated with epigenetic differences in a cohort of research subjects called "pSoBid" – psychological, social and biological determinants of ill health (McGuinness et al. 2012). The study found that the most economically deprived subjects had, in their peripheral

blood, 17% less DNA methylation globally[50] than the affluent subjects, and that manual workers had 24% less DNA methylation content than non-manual workers. Associations were also found between DNA methylation levels and previously established biomarkers of cardiovascular diseases and inflammation, such as fibrinogen and interleukin 6.

This research focuses on the McGuinness study and the city of Glasgow where the study took place for several reasons. First and foremost, the cohort used in the study was designed from the beginning to study socio-economic differences in relation to health outcomes (Velupillai et al. 2008), thereby providing empirical ground for exploring how epigenetics is recruited as evidence in studies on social inequalities in health. Second, the study was triggered in response to health inequalities in Glasgow illustrated by the difference of 26 years in the average life expectancy between Glaswegians from the most deprived and the most affluent area (WHO 2008). More specifically, these stark health disparities could not be explained by conventional risk factors, as other post-industrial cities with similar socio-economic profiles, like Manchester or Liverpool, do not show such a steep gradient in health. The health figures that had "earned" the city of Glasgow the reputation of 'the sick man of Europe' also defined the contours of a true unknown within the well-rehearsed framework of the social determinants of health; and led to the naming of such phenomenon as *the Glasgow effect* (WHO 2011). Third, the pSoBid cohort, and accordingly the McGuinness study, were initiated by a local health organisation, the Glasgow Centre for Population Health (GCPH), and gathered people of various

[50] DNA methylation levels are an epigenetic mark that is, according to the authors of the study, 'reflective of changes in gene expression linked to disease'.

backgrounds – from social epidemiology and occupational health, to biochemistry, genetics, biological aging and epigenetics, to psychology, and neuroscience – to work together and collectively gathering the data and propose action to address the prevailing heath inequalities in Glasgow. Finally, the results of all studies, including the McGuinness study, were collectively presented in a report, which its proponents offered as a guide for Glasgow's public health policies (GCPH 2013).

Materials and methods

The empirical investigation of the McGuinness study, the pSoBid cohort and the city of Glasgow – to which I will refer collectively to as 'the Glasgow case' in further text – included: a review of publications produced on the pSoBid cohort, and activities and projects of the GCPH who initiated it and semi-structured interviews conducted in Glasgow with eight professionals involved in the pSoBid project. Additionally, two observational studies – one in Glasgow, other Milan – were included into the analysis of the Glasgow case, after it became evident that football supporting in Glasgow, and the social activities related to football supporting, provide an important, if not a decisive insight, into the relations among researchers and participants of the pSoBid study, and among Glaswegians in general.

The two main themes interrogated by the semi-structured interviews include: 1) how do different agents cooperate to bring about healthcare policy; and 2) what is the evidential value of epigenetic data in public health. Several additional questions within these two broad themes were also examined: how actors from

different professional/disciplinary background came to collaborate in the first place; how these actors understand, interpret, value and use epigenetic evidence; how is epigenetic evidence used and understood in comparison to other (non-molecular) types of evidence in public health (i.e. data coming from social epidemiology). For details on how the Interview Guide was designed and interviews conducted, see Chapter Three – Research Design and Methods. The initial coding in thematic analysis suggested that communal identity and membership is a theme that cuts across all others. The full significance of the communal identity and membership in Glasgow was recognised upon complementing the interview data with observations made during social activities initiated by football supporting.

COLLABORATION AMONG ACTORS OF DIVERSE BACKGROUND

Despite the diversity of expertise in the pSoBid project, all interviewed members expressed a shared perspective on how their collaborative endeavour was established, and how 'health' is understood within the endeavour. The common response to the question of how collaboration between the team members began was that the interviewees were initially exposed to each other's work through talks and seminars organised by the institution to which all the interviewees belong – the University of Glasgow. This exposure was perceived as providing them with an opportunity to exchange ideas, involve more colleagues and co-workers in the process, and develop a common vision that would eventually be formalised through shared projects.

Two main components can thus be distinguished as having played a role in the establishment of this collaborative platform: institutional and personal component. Institutional facilities were understood as providing geographical proximity of (most) researchers involved in the project and hence as facilitating an informal engagement between different professionals. At the same time, the home institution (the University of Glasgow) is perceived as facilitating people's exposure to each other's work in a more formal way, by organising different social events and seminars. On the other hand, people's personal character and willingness to take part in a long-lasting project that gathers people of very different disciplinary backgrounds emerged as additional and major facilitator of the pSoBid project. Several interviewees pointed out that the pSoBid project depended also on people who are neither constitutive collaborators nor institutional affiliates but whose engagement was nonetheless essential for the project.

One such example is the pSoBid cohort research participants. In particular, the participants from the most deprived community and spanning the 25-35 years age range, were difficult to recruit in the first place. In this case, the personal character of the individuals involved in the project, and their capacity to 'bring people together' from the local *communities* was indicated as the 'engine behind' the successful implementation of the project. Another such example of non-constitutive members playing an essential role in the implementation of the pSoBid, are officials from the local authorities. Although the local authorities as a body represent a constitutive member for projects' implementation, the officials hold elected positions. The ways in which the research project was presented to the current officials from the local authorities was therefore critical for a

successful implementation of the project. Communication skills and *personal* 'engagement with local authority officials' were singled out as making the difference between positive and negative answer to perform a certain study, as exemplified by the following statement:

> "Member 9[51] had done an amazing job to translate messages of the research to wider audience including policy-makers. He has been involved from the beginning in the pSoBid, the [Glasgow] Centre [for Population Health], and knows epigenetics and biological basis [of aging and health outcomes]" (Member 6).

The interviews revealed also a shared perspective on two added values at the basis of their collaboration. First, the interviewees pointed to the existence of a community problem, i.e. the steep health inequalities that map onto social inequalities between Glaswegian communities, which they defined as "the glue", or "a unifying thrust" under which people joined forces to address this problem. Second, all interviewees emphasized that a holistic approach to the process of aging and health in necessary to be adopted in order to tackle the underlying factors across all aspects of people's lives that affect healthy aging.

In order to fully appreciate how Glasgow's community problem constituted a major driver for the establishment of collaboration in Glasgow, the unique historical background and current political situation of its citizens need also to be taken into account. The Irish ancestry of many Glaswegians, and most notably

[51] The interview that was scheduled with Member 9 had to be cancelled.

those living in the deprived parts of the city, contributes to a strong sense of 'immigrant community' in relation to their national identity and sense of belonging to the United Kingdom. One of the interviewees pointed out how the following statement by former conservative London Mayor set a furious reaction: "a pound spent in Croydon [South London] is far more of value to the country than a pound spent in Strathclyde [in the Glasgow area]"[52].

Glasgow's public attitude towards the central government was reflected by the electoral results of the Scottish Independence Referendum in 2014, when the majority of Glaswegians voted for independence. According to the interviewees, the distance between the community of Glaswegians and the central politics of the UK resulted in huge public support of local initiatives, such as the pSoBid project, and other related projects such as GCPH's Glasgow Indicators project or Medical Research Council's the West of Scotland Twenty-07 study. The communal identity and membership of Glaswegians had, in fact, a significant impact on the recruitment of participants for the pSoBid study. Recruiting the participants was, of course, crucial for initiating the study in the first place.

> "It was...[shaking head]. Member 10 and I had to talk to the guys before and after games, in the pub..." (Member 1)

The 'games' this statement is referring to are the matches of Celtic football club (FC). The recruitment of participants from the deprived area was conducted, in part, at the Celtic Park football stadium. As the matter of fact, the topic of recruitment during the fieldwork in Glasgow was first discussed in an informal

[52] See: https://www.youtube.com/watch?v=CjFboRwGiqc (Last accessed: 09/09/2016).

conversation that took place on the road from Dalmarnock railway station and Celtic Park football stadium. Walking the road from Dalmarnock station to Celtic Park, I was told that this was the deprived area from which the participants of the pSoBid came. Walking through this area of Glasgow is generally not recommended. The housing projects have improved the infrastructure of the area in the past several years, but their effects are slow to detect – the health has improved too little compare to what the decision-makers consider is worth further investment. This was pointed by several interviewees as the main issue in delivering long-term health interventions and why initiating collaborative projects that collect as much evidence as possible, like the pSoBid, is of the utmost importance for the community. On the match nights, however, the area is safe as *everyone* is walking together to reach the Celtic Park, chatting and singing the club songs – people from Calton, the deprived area, professionals like member 1 and 2 (who happens to live in the affluent area of Lanzie), and many other Glaswegians. It was this 'local' and 'inside experience' of football supporting activities in Glasgow that, in fact, provided a deeper appreciation and understanding of the interviewees' insistence on the community and its problems as the 'glue' of their endeavour.

A couple of months later, in Milan, I joined the Celtic supporters, including the pSoBid researchers, for another game, this time at the San Siro stadium in Milan – Celtic's match against Internazionale in the Europa League. What has been observed about the Celtic supporting Glaswegians, from the activities that preceded and followed the match, to the match itself, seemed to be reflecting the description about the community expressed by one of the interviewees: "We are very tribal" (Member 1). Moreover, the Irish ancestry and the present-day

inclination to everything-Irish, painted everything at the San Siro stadium and across the city of Milan into green and clovers, while the flag of Ireland was hoisted on each step. A remark that not a single Scottish flag was present was met with a "we are an Irish Club" response from several of the supporters. These observations and 'lived experience' of what the Celtic represents for the Glaswegian community beyond just being a football club, lead to the revisiting of the data collected through the semi-structured interviews in Glasgow and to the inclusion of these observational data into the analysis of the Glasgow case.

What might seem as a trivial detail at first glance – a sport club membership shared by both study participants and researchers – played instead an important role in the development of the pSoBid project, and hence constituted an important resource for the analysis of Glasgow. In other words, beyond the simple fact that the deprived community and (the more affluent) researchers are gathered around the same football team, lie in fact the norms and values that, made possible the assemblage of the collaborative approach of the pSoBid project to the local health conditions of Glasgow. The local 'morality' of Glasgow manifested itself in a sense of belonging to a football team and in its supporters' relation to the rest of the country and provided a fertile terrain for aligning a moral investment into the long-standing injustices affecting Glasgow citizens with a number of sentiments and aspirations. These sentiments and aspirations were expressed as deontological claims of professionals from the pSoBid to provide knowledgeable representations of such injustices that would bring about political action, and as an expression of trust in and commitment to this research on the side of research participants. It is the particular social and political character of the context of Glasgow – characterised by historical legacy

of migration and political conflicts, as well as the current distinct identity in relation to the rest of the UK – that catalysed and shaped this kind of collaborative research practice around epigenetics.

Collaboration in Glasgow is thus grounded in specific relationships – local bonds – between the members of this community and can, accordingly, be characterised as 'shared practices that reflect a collective commitment to carry some costs to assist others' (Prainsack and Buyx 2011). In other words, the collaborative in the case of Glasgow can be considered a solidaristic endeavour. The costs of assisting others can be reflected as career-related for researchers, as they agree to give addressing the communal problem a higher priority in their work; the cost of inconvenience in providing biological samples for research participants; and financial cost of supporting publicly funded projects and initiatives like the pSoBid for the Glaswegian citizens in general. Moreover, the practices entailed in the pSoBid project are enacted on different levels: personal, communal and contractual (Prainsack and Buyx 2012). The personal level is exemplified by the collaboration between the members of the pSoBid team. Solidarity is thus enacted among the researchers as they carry time- and resource-related costs for pursuing a collective commitment to interdisciplinary, collaborative research rather than to their own. The communal level is exemplified by the recruitment of participants, which was facilitated by the fact that both researchers and participants belonging to specific community – the community of Celtic FC supporters. Moreover, communal solidarity is reflected also in community's support, including in funding, to the local health initiatives like the pSoBid, Finally, the contractual/legal level is exemplified by the very establishment of the Glasgow Centre for Population Health (GCPH). The GCPH

represents a contractual commitment to take action on health inequalities in Glasgow between the Scottish Government, the National Health Service Greater Glasgow and Clyde, the Glasgow City Council and the University of Glasgow. The practices engendered by a distinct context of Glasgow, grounded in and brought about by social relations among Glaswegians – as researchers, participants, or simply citizens – thus reflect a shared commitment to carry costs to assist others. In other words, they are solidaristic. The Glasgow case thus represents an empirical example of the initiation and implementation of a collaborative health project through solidarity.

EPIGENETIC DATA IN HEALTH RESEARCH AND POLICY ACTION

The role of epigenetic knowledge in capturing and intervening upon the socio-political aspects of the 'Glasgow effect' emerges from the interviewees' diverging responses to questions regarding the status of epigenetic evidence in social action and public policy (compared to other, non-molecular types of evidence), and the extent to which epigenetics is expected to influence, or perhaps even change, research on socially-affected health phenomena and policy strategies that may be devised based on such knowledge.

All interviewees emphasized that adopting a holistic approach to the process of aging and health is necessary in order to tackle the underlying factors across all aspects of people's lives that affect healthy aging. Epigenetic data was here understood as providing an additional layer of information, contributing thus to a deeper understanding of the interconnectedness between factors that influence health and aging, and opening additional possibilities for intervention.

However, the interviewees perception about the value of epigenetic evidence, compared to the already available evidence gathered through the means of classical epidemiology, i.e. non-molecular data, differed in relation to whom was such evidence presented.

With respect to health research, epigenetics was mostly understood as an additional measure reflecting allostatic load, or as 'bio-dosimeter' (McGuiness et al 2012; Landecker and Panofsky 2013). As the geophysical and demographic maps of Glasgow are already available, together with historical data about population migration and settlements, the demonstration of environmental effects on health is sought also on the molecular level, measured within the body. Epigenetic data is thus understood as making a contribution to research and action upon health insofar as it can be easily converted into the current standard measure in epidemiological research – the quality adjusted life years (QUALYs).

> "There is no hierarchy of evidence ... no special status for any particular type of data... It can happen that one type of evidence suggests different and/or contradictory conclusions [and] epigenetic data can influence hypothesis generation to great extent and the methodological set-up of population health research" (Member 5)

The representative of the GCPH pointed out that before the pSoBid study, there was no such 'all encompassing' effort present in population research in Glasgow and that adding the 'biological component' into the investigation of the determinants of ill health 'definitely provides deeper insight into factors that

contribute to ill health'. As for the influence of this data to the ways population research is being conducted, the same interviewer stated:

> "I don't think it [epigenetic data] is more important. The [Glasgow] Centre [for Population Health] is definitely taking the biological element into consideration [but] it is not separately included in the agenda of the Centre [and] our research will continue to use the traditional approach. But the biological level will be kept in mind for future projects" (Member 6).

These data suggest that the collaboration with the pSobid that relied on both the biological, i.e. epigentic data, and data collected through the methods of classical epidemiology, was not characterised as redrawing the boundaries between the disciplines. Similarly, the collaboration was not understood as providing a whole new conceptualisation of social phenomena to affect political decision-making in public health. Rather, epigenetics is understood as a potential resource in overcoming some disciplinary limitations that people are faced, a boundary concept (Star and Griesemer 1989). The head of the lab expressed this attitude while pointing out that everything they do in the lab has a strong translational emphasis and must be applicable to real population as well.

> "Things often work in the lab, but then are not so good when they 'leave' the lab and are supposed to 'meet' the real populations. [Our] work is directed towards validation and application of biomarkers of aging we

identified in the lab in clinical populations and epidemiological cohorts. ” (Member 1)

On the side of social epidemiology and public health, this was expressed in terms of the influence that utilization of epigenetics can have on ‘scalability of research’ and ‘study design’. The head of the Healthy Working Lives group pointed out that in order to make the data reliable, the classical population studies have to be large-scale, with big samples, over longer periods of time. Studies collecting the data on molecular level, like epigenetic studies, can significantly reduce the size of the sample necessary to conduct a study, and the time needed to obtain reliable evidence and to devise and implement intervention strategies.

The molecular approach in epidemiology is thus understood not as overriding the classical epidemiological approach but as making a difference in providing support for some existing health strategies over the others. Epigenetic data is thus considered as a practical, advantageous tool in discriminating between more effective and less effective interventions at more early stages of their implementation, which can also be used for long term monitoring to validate the success of health interventions.

“You test for more hypotheses at the same time... Epidemiological studies are large-scale, takes long to get results and know if you are successful... here [in the lab] you test on a small sample, get results faster... it reduces time, size and cost”. (Member 2)

The representative of the GCPH, reflected upon the pSoBid collaborative endeavour as potentially opening up different disciplines to the tools and approaches of the other:

> "A collaborative and multifactorial approach can open up a horizon for policy makers to take into account this new form of evidence, but also for [lab] scientists to reach out to the field of population health and policy [making] with their own research data".

Yet, the potential of the new, molecular, was recognized mostly in relation to its purported objectivity. Molecular type of data is therefore recognized as 'silver bullet', or a 'sought for' type of evidence in fostering political action upon health and social inequalities in health in Glasgow.

> "I was looking for a way to approach policy people, make them more interested [in the work I was doing]... they are sceptical about small scale results [in epidemiological research] but say that the population is too big to make such studies and interventions" (Member 2)

In this respect, epigenetics could be considered as a novel lens, the molecular and hence objective conduit (Landecker and Panofsky 2013) that lets decision makers see things for what they really are, all the more so when they are buried 'under the skin', thereby escaping the eye of everyman (Jasanoff 1998).

> "[It] is considered more objective... surveys are still considered to be 'soft version' of the data, too subjective... [this] is physical. Decision-makers can see, directly, how things get under the skin." (Member 7)

Epigenetics is thus understood as an instrumentally effective, policy-tied kind of knowledge that could foster socio-political change in a non-distant future largely by virtue of its purported objectivity. The potential for political action assigned to epigenetics therefore stems from its translation of the social environments (e.g. class, biography, community membership) at the basis of "the Glasgow effect", into a different kind of material objectivity, whose molecular representation is deemed to offer better leverage for socio-political change. The mobilization of epigenetics in the collaborative health endeavour in Glasgow points therefore to a moment of intertwined epistemic and normative self-reflexivity. It is the political aspirations that inform policy-relevant health research and thereby recruit a specific kind of knowledge, along with its practitioners, in light of its promised potential for health-related policy-making.

CONCLUSIONS

The empirical data presented a case of how the community issues related to inequalities among and local bonds between Glaswegians played a pivotal role in assembling the collective endeavour of the pSoBid project; and how the interdisciplinary context of the Glasgow case curved a space for epigenetic evidence in a research agenda aimed at social policy change.

It is, indeed, from the problematic socio-political background that yielded "the Glasgow effect" that the epistemic dialogue among the disciplines around epigenetics emerged. A shared *historical* legacy of migration and political conflicts, as well as the *current* immigrant and distinct identity in relation to the rest of the UK, that characterize the context of Glasgow, appear to be the driving engine of health endeavours like the pSoBid. Within such a context, epigenetics emerges as an epistemic, techno-scientific articulation of the local morality shared by the Glaswegians as supporters of a football team, researchers, or simply citizens, which the statements like 'we are very tribal' epitomize. The local 'morality' of Glasgow manifested itself as belonging to a football team, and in its supporters' relation to the rest of the country (as many of them are descendants of Irish settlers from the 19th century onwards), provided a fertile terrain for aligning a moral investment into the long-standing injustices affecting Glasgow citizens with a number of sentiments and aspirations. The sentiments of being first and foremost Glaswegians translated into deontological claims of professionals from the pSoBid to provide knowledgeable (molecular) representations of such injustices for policy-makers. From their perspective, leveraging the virtue of the purported objectivity afforded by epigenetics is to contribute to a socio-political change in a non-distant future, which could finally remedy to the past injustices affecting their fellow supporters and citizens. On the side of the latter, Celtic's membership and belonging to its community of supporters translated into an expression of trust in – and a commitment to – this research, which made possible the recruitment of a sufficient number of participants to these studies from the more deprived communities.

A ‘molecular heuristic’ of the social and material causes in Glasgow thus seems to be propelled and shaped by the aspirations to remedy the infamous title of “the sick man of Europe” and a moral enterprise that emerges from it. In such an enterprise, the Glaswegian biologies enable temporary joint epistemic work (Niewhoener 2015) and the construction of mixed epistemic categories (Meloni 2015) among researchers gather around the pSoBid, in their endeavour to address the environmental and social determinants of health. Differently from the understanding that epigenetics is used for assigning responsibility for the bodily effects to the individuals who fail to comply with environmental advisories instead for socio-political action on pre-existing inequalities in health (Mansfield 2012), the openness to the environment and the molecular representation of its effects on individual health are in the case of Glasgow regarded as a potential “game-changer” for the resolution of the long-standing inequalities that characterize the health of Glaswegians, including and particularly on the level of political action. The potential for political innovation assigned to epigenetics stems precisely from its translation of the social environments (e.g. class, biography, community membership) at the basis of “the Glasgow effect”, into a different kind of material objectivity, whose molecular representation is deemed to offer better leverage for socio-political change.

The mobilization of epigenetics in the collaborative health endeavour in Glasgow thus points therefore to a moment of intertwined epistemic and normative self-reflexivity. The recognition of the instrumental role of epigenetics in the case at hand does not however diminish its heuristic potential. The research around epigenetics currently embeds diverging representations of biological phenomena (e.g. an additional layer of evidence, a type of material objectivity, etc.), and

allows distinct types of joint epistemic works (Niewhoener 2015) within the community of natural scientists, epidemiologists, sociologists, anthropologists, psychologists, etc. However, rather than testifying to thicker conceptualisations linking biology and culture (Niewöhner 2015), the case of Glasgow highlights the very concrete ways in which the epigenetic *factual* discourse can come to operate that analogi-digital translation of material (food, occupational exposures, toxins, pesticides) as well as social (chronic stress, social status, early life adversity, parental behaviours) environments into the language of epigenetic markings (Meloni and Testa 2014). The epidemiological uptake of epigenetics, however, occurs insofar as its data can be made compatible with their own standard of coding – the QUALY, through its translation into genome-friendly form. Regardless of whether it is genome-friendly or QUALY-based, the instrumental value of epigenetics arises through its provision of a decontextualized snapshot of molecular endpoints that sample the social and environmental turmoil of human existence (Lock 2015). In doing so, it thus turns the understanding of complex cultural and social practices into molecularly accountable interacting substances that get under our skin (see Landecker 2011, Landecker and Panofsky 2013). It is thanks to its molecularization of the environment that epigenetics is bestowed the potential for actionable public health knowledge.

At the same time, the case of Glasgow represents also an example of how successful implementation of a collective endeavour rests upon the local bonding and social relations between researchers and participants who both are first and foremost fellow citizens. The case of Glasgow thus provides an empirical example of solidarity as grounding principle of research and for bringing about

political action upon health. The context of Glasgow is, indeed, a rather specific one. The norms and values that made possible the assemblage of health endeavour like the pSoBid might, in fact, be endemic to Glasgow. In this sense, the applicability of a solidarity-based research and action upon health in some other contexts might prove to be challenging. Nevertheless, the Glasgow case indicates that 'increasing our sensitivity to the particular details of the pain and humiliation of other, unfamiliar sorts of people... makes it more difficult to marginalize people different from ourselves' (Rorty 1989, p. xvi). Accordingly, as the case of Glasgow suggests, if not on the global level, it certainly can propel political action in local communities.

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CHAPTER SIX – CONCLUSIONS

This project was an empirical invesriation of epigenetics and its societal implications. Starting from a mapping of the field activity, this research has first shown that epigenetics is most actively studied in cancer, cardiovascular diseases, neurodegenerative diseases, autoimmune diseases and diabetes. Epigenetics is actively employed not only in basic research but also in translational and clinical research. Moreover, numerous drugs with epigenetic mechanism of action are in use for treating diverse types of cancer – glioblastomas, leukemias, lymphomas, etc., while many epigenome-modifying compounds are currently being tested in cancer and other diseases. In aiming to answer to the research questions of what are the most active types of epigenetic research; what are the most actively studied disease areas, areas of clinical application and what are the research outputs of epigenetic research, the thesis found that the disease areas most actively studied in epigenetic research, and where its clinical application is most detectable, are precisely those areas that the public health agencies like the WHO and the political bodies like the EU

identify as posing major challenges to the health of the population (WHO 2008; 20012; EU 2007).

At the same time, these diseases have long been known to be, or at least suspected to be, influence by environmental, social and life style related factors. In line with this, the big epigenetics consortia that have been established in recent years state among their objectives the understanding of how epigenome has shaped human populations over generations and in response to the environment, and how exposures such as physical, chemical, behavioral, and social factors influence gene expression and health. However, most of their published data do not even contain the word 'environment', Instead, the expressions employed are exclusively those from genomic vocabulary, e.g. functional annotations, datasets, regulatory networks, mapping, etc., suggesting thus that the environment in epigenomics – the dominants practice of today's epigenetic science – is being taken into consideration insofar as it is, and could be, converted into 'genome-friendly and code-compatible' digital readouts (Maloni and Testa 2014).

A much small corner of the field that is concerned with the causal relationship between factors such as chemicals, smoking, diet, exercise, etc., and health-related conditions like elevated blood pressure, anxiety, obesity, and goes by the name environmental epigenetics. The experimental formulization of environment in environmental epigenetics generates concept of the environment as being moleculairzed. Molecularisation of the environment, accordingly, is the aspect of epigenetics that resonates well with wider society's aspirations of 'taking control of your health' (Reliv International) and 'your DNA is not your

destiny' (Cloud 2010; Spector 2012), as well as with social inequalities in health paradigm (McGuinness et al 2012) and hopes of new engagement between the social and the biological sciences (Landecker and Panofsky 2013; Meloni 2015; Niewhoener 2015). It is precisely this small subfield in epigenetic research that has been gaining attention in diverse domains beyond biomedicine, despite, or perhaps even because, its results are disputed within biomedical research community.

Focusing on one interdisciplinary project based in Glasgow – a city characterized by stark health and social inequalities, where epigenetics has been employed to measure and instruct relevant social programs to target these inequalities – this research has further shown that it is the community issues related to inequalities among, and the local bonds between, Glaswegians that played a pivotal role in assembling the collective endeavour of this interdisciplinary project. Moreover, it is precisely from the problematic socio-political background that yielded "the Glasgow effect", that the epistemic dialogue among the disciplines within the project emerged. Within such a context, epigenetics emerges as an epistemic, techno-scientific articulation of the local morality shared by the Glaswegians as supporters of a football team, researchers, or simply citizens, to remedy for the perceived long-standing injustices that community had endured. In aiming to answer to the research questions of how is epigenetics mobilized and conceptualized by actors of diverse backgrounds involved in an interdisciplinary collaborative project, this thesis found that within such one project – the pSoBid project – that aimed to measure and instruct relevant social programs to target health and social inequalities, epigenetics is perceived to be an instrumentally

effective, policy-friendly evidentiary resource that could foster socio-political change in a non-distant future. Accordingly, it is thanks to its molecularization of the environment and therefore its purported objectivity, that epigenetics is bestowed the potential for actionable public health knowledge.

The expectations of epigenetics seem to operate on two levels. First, epigenomics is expected to deliver where its –omic predecessor genomics has faild to do so. However, epigenomics goes 'beyond the genome' only insofar as the environmental, the social, the biographical – the 'analogical vastness of the environmental signals' – can be converted into 'genome-friendly and code-compatible digital representation' (Meloni and Testa (2014). Differently than in the life sciences and biomedicine, this 'code-compatibility' in epidemiology is predicated upon the conversion of epigenetic data into the standard code used in epidemiological research – the QUALYs.

The instrumental value of epigeneticist thus arises through its provision of a decontextualized snapshot of molecular endpoints that sample the social and environmental turmoil of human existence (Lock 2015). In doing so, it turns the understanding of complex cultural and social practices into molecularly accountable interacting substances that get under our skin (Landecker 2011, Landecker and Panofsky 2013). In relation to this, epigenetics is expected to also provide insight into how the contingencies of life – what we eat, pollution or stress – affect how genes operate. In other words, how the environment, biography and milieu are molecularly embedded to produce bodily outcomes body (Landecker 2011; Niewhoener 2011; Mansfield 2012; Meloni 2015).

The research around epigenetics currently embeds diverging representations of biological phenomena (e.g. an additional layer of evidence, a type of material objectivity, etc.), and allows distinct types of joint epistemic works (Niewhoener 2015) within the community of natural scientists, epidemiologists, sociologists, anthropologists, psychologists, etc. However, rather than testifying to thicker conceptualisations linking biology and culture (Niewöhner 2015), the case of Glasgow highlights the very concrete ways in which the epigenetic *factual* discourse can come to operate the translation of the material (food, occupational exposures, toxins, pesticides) as well as social (chronic stress, social status, early life adversity, parental behaviours) environments into the language of epigenetic markings (Meloni and Testa 2014). Moreover, differently from the understanding that epigenetics is used for assigning responsibility for the bodily effects to the individuals who fail to comply with environmental advisories, instead for socio-political action on the pre-existing inequalities in health (Mansfield 2012), the openness to the environment and the molecular representation of its effects on individual health are in the case of Glasgow regarded as a potential "game-changer" for resolution of the long-standing inequalities that characterize the health of Glaswegians, particularly so on the level of political action.

This thesis shows that in the case of Glasgow, the potential for political innovation assigned to epigenetics stems from its *translation* of the social environments (e.g. class, biography, community membership) at the basis of the "Glasgow effect", into a different kind of material objectivity, whose molecular representation is deemed to offer better leverage for socio-political change. In this respect, the Glasgow study exemplifies a more general trend in population studies

towards the collection of biological samples and increasingly sophisticated biomarkers analysis. Emergence of such a trend coincides with increasingly voiced complaints about the lack of political commitment and action to tackle social determinants of health despite the vast amount of evidence collected in previous years by means of classical epidemiology. The recent "Review of social determinants and the health divide in the WHO European Region: final report" (WHO 2012) was, in fact, portrayed as "a 'wake-up' call to action among political and professional leaders" by the WHO Regional Director for Europe (page v, *Forward*). The Review followed up on the final report (WHO 2008) of the Commission on social determinants of health established in 2005 after decades of research into social determinants of health, that was launched on the bases of calls for action expressed in the WHO Declaration of Alma Ata Declaration in 1978 and the Ottawa Charter for Health Promotion in 1986. Finding the evidence of molecular embodiment of social factors such SES and poverty thus features as a potential game-changer in the policy-making arena in general.

This thesis delivers an empirically grounded contribution to explorations of epigenetics. In pursuing its first aim – mapping the impact of epigenetics on health care – this thesis makes a methodological contribution to empirical investigations of emerging fields of the life sciences. The thesis delivers a combinatory qualitative-quantitative method for systematic scoping of data to produce a map of the most active areas of research and clinical application of epigenetics. Furthermore, by focusing on the case of Glasgow, a city characterized by stark health and social inequalities, where epigenetics has been employed in a interdisciplinary project to measure and instruct relevant social

programs to target these inequalities, this thesis contributes a critical insight into how is epigenetics is *currently employed* – in collaboration between actors of diverse backgrounds; and in policy efforts and action upon health. It thus contributes to discussions about epigenetics and molecularization of the environment, biography and milieu (Landecker 2011; Niewöhner 2011; Mansfield 2012) by adding an understanding of epigenetics as an instrumentally effective, policy-appropriate evidentiary resource that could prove a "game-changer" for the resolution of the long-standing inequalities that characterize the health of Glaswegians.

The thesis also contributes to discussions about the governance of research. It delivers an empirical example of how solidarity practice lied at the basis of an interdisciplinary collaborative research project and operated to bring about political action in local communities. Solidarity has previously been discussed as a practice of citizens towards research biobanks whereby citizens should accept a small cost of sample donation as their trust in and commitment to research that in the future could benefit the whole of society (Prainack and Buyx 2013); and towards other citizens in accepting that those who suffer from the so-called 'life-style related diseases' – like smoking induced lung cancer – should not be denied access public health services on the bases of their solidarity with people who do not 'practice' such 'unhealthy life styels' (Buyx and Prainsack 2012). This thesis has shown that solidarity practice need operate also on the side of scientists towards the citizens and community they belong to. In discussion on public 'unease with' and 'lack of trust in' science (EC 2007), the thesis shifts the focus away from 'democratization of expertise' and 'citizen science' standards and questions of legitimacy and extension (Collins and Evans 2002) and

representation (Brown 2009). The thesis, instead, suggests that it is the local bonds between of citizens of Glasgow, where scientists are at the same time first and foremost citizen of their local community, which played a decisive role in initiation and implementation of an interdisciplinary collaborative research project. Thus, this thesis invites further explorations of solidarity practices and the role of 'scientist as citizens' in discussions about the governance of research.

Finally, being grounded in a programme of interdisciplinary character, this thesis is uniquely positioned to make a trans-disciplinary reflection upon epigenetics and its societal implications. Hence, this thesis stands as a piece of interdisciplinary scholarship that found its place within the field of STS – a field that has long been openly friendly to such contributions. The interdisciplinary character of the thesis is reflected in the aims it set to achieve, methods it employed and disciplines it relied on, and presents its greatest strength.

On the other hand, it presents also the source of its limitations. First, the two aims it pursued in parallel are not incompatible but there is a tension between them in terms of both empirical methods and theoretical assumptions that informed them. This thesis did not attempt to solve them but rather embraced them as valuable insights to and reflections of how epigenetics has come to inhabit different social worlds and different fragments of social reality. With respect to this, however, the thesis does bring to the fore the difficulties with which projects responsible to simultaneously contribute to different communities face. In the case of this project, it is the biomedical research community, as exemplified by its research activities conducted for the EPIGEN project; and humanities and social sciences, as exemplified by this research

activities conducted within the program of Foundations and Ethics of the Life Sciences and Their Ethical Consequences. Accordingly, the experimental character of this thesis represents an important exploratory contribution to interdisciplinarity as mode of inquiry.

Second, and in relation to the first, this thesis was faced with bureaucratic impracticalities in sampling procedure and funding limitations for the fieldwork in Glasgow, which was reflected in the small sample of people who were interviewed. Although this in no way affected the quality of the data collected, accessing a greater number of people would have certainly been beneficial for the thesis. Moreover, the project focused on one distinct local context. Although the specificities of Glasgow represented an interesting object of inquiry, investigating how they relat to the more general practice of epigenetics in research on social inequalities in health would have also been beneficial for this thesis. Accordingly, one way in which the research informed by this thesis can be directed in the future is precisely to explore normative and epistemic tensions and junctures that arise from understanding of the human body as both universal and locally embedded. A recently established "Epigenetics and Stress Network" (EpiStressNet[53]) gathers researchers of diverse background and various institutions across the UK and Europe (including some pSoBid researchers) to 'elucidate the biological impact of social and behavioural stressors'. An observational study of meetings, supplemented by interviews with various partnerts in the network, would indeed provide an ideal terrain for the exploration 'joint epistemic work' (Niewöhner 2015) and 'mixed epistemic categories' (Meloni 2015) as well as normative concerns brought about by

[53] Available at: https://www.sheffield.ac.uk/epistressnet (Last accessed on 12.12.2016)

molecularisation of the environment, biography and milieu (Landecker 2011; Niewöhner 2011; Mansfield 2012).

Additionally, after an initial exchange of ideas at the PhD training School in York, Anna Lydia Svalastog (Østfold University College, Norway) and I explored 'gender as cause and effect' in the science of epigenetics and discussed the importance of gender analysis for research design and interdisciplinary dialogue in science and public debate (data presented at the Symposium Body Discourses / Body Politics and Agency: What's Left of the Body, Vienna, 5-7 February 2015). Due to necessity of prioretizing between my already numerious project commitments, this promising terrain for investigation had to be left aside for some future projects. Hence, another way in which the follow up research of this project can be taken is to further investigate of how gender is (not) informing research design and interdisciplinary dialogue in science and public debate.

Finally, in an essay required for completing the PhD course in "Foundations of Probability and Statistical Inference", I discussed how stability vs. reversibility of epigenetic marks would (re)configure the understanding of 'risk' in epidemiological research, depending on the choice of statistical inference – frequentist ('objective'; based on a series of repetitions; fixed) or Bayesian ('subjective'; based on degrees of belief; dynamic). As my interest in the philosophical foundations of science has always been strong, further exploration of the conceptual issues in epigenetic data collection and analysis in population studies, and their social dimension, would be another potential direction of future research on epigenetics and policy.

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