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Innovation cycles and geographies of innovation: A Study of healthcare innovation in Europe

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This paper examines place-specific factors affecting geographies of innovation, that is, the transfer of research from the laboratory to bedside in the healthcare sector in four European bioscience regions. These regions are Medical Delta (MD, Leiden, Rotterdam and Delft, Netherlands) Oxford and the Thames Valley, (OTV, UK), Biocat (Catalonia, Spain) and Life Science Zurich (LSZ, Switzerland). Evidence is drawn from the EU funded HealthTIES project (2010-2013). The analytical framework, the HealthTIES Innovation Cycle, is organised into resources (inputs), innovation system elements, and outcomes. The paper shows that each region represents different positions within international value chains of innovation in the healthcare sector. They range from the highly research intensive but with relatively less in the way of commercial exploitation location (OTV) to the less research intensive but with more commercialization (LSZ).

1. Introduction

In the study of innovation geographies, place-specific factors come together to enable firms and other kinds of organisation to undertake radical, new, and/or incremental product, service and process development. As Feldman (2014) points out, while investments in innovation in certain places yield jobs, growth and prosperity; similar investments in others fail to produce the desired local effects. The focus in this paper is on how innovation is organised at the local

level in the healthcare¹ field. In so doing, we identify the elements of innovation cycles and the resulting outcomes in often internationally organised innovation value chains, where value is realised in these locales.

Our study draws on data from a recently completed EU FP7 funded study (2010-2013) -- Healthcare Technology and Innovation for Economic Success (HealthTIES). The organising framework for analysis used is the 'Healthcare Technology Innovation cycle'. The study is based on four European regions: Medical Delta (MD; Leiden, Rotterdam and Delft, Netherlands) Oxford and the Thames Valley, (OTV; UK), Biocat (Catalonia, Spain) and Life Science Zurich (LSZ; Switzerland) along with an emerging region, Debrecen (Hungary)². The regions are all leading centres in healthcare innovation in their own country.

However, 'regions' are complex entities differing in scale; they are not only administrative entities but can be functional regions built for a particular purpose. The EU's own concept of 'region' is flexible. "Regions" are defined in the broader sense such as Länder, communities, autonomous communities, departments, provinces, counties, metropolitan regions and any other political entity with relevant competences to accomplish their engagements³. Our 'regions' vary in size and in the composition of their research and industrial bases, as well as in their administrative and functional status. Therefore in the analysis, we consider all parallel developments in order to reflect on diversities of value chain development at a given moment in time, rather than on systematic comparisons.

¹ Healthcare is defined broadly to incorporate life sciences and other sciences resulting in the development of diagnostic, therapeutic, and convergent technologies. The sector includes drug development, diagnostic businesses and other therapies.

² HealthTIES: Healthcare Technology and Innovation for Economic Success

³ http://cor.europa.eu/en/takepart/eer/Documents/EER_Leaflet_2013_EN.pdf

Within this varied geographic context, we address the following research question: how has the innovation cycle in the healthcare sector developed in each of the four regions? We argue that it is necessary to look beyond just universities and the biomedical industry sector to map the elements of the cycle in order to account for individual regions' differing strengths, weaknesses, and prospects. To contextualize the research question, we define the innovation cycle and examine explanations for particular geographies of innovation. This is followed by the profile of each of the four regions, the methodology used to assess performance, and the data analysis. Finally, some conclusions are drawn on what has been learned about regional differences and the implications for prospects for future developments.

2. Innovation cycles and innovation systems in healthcare at the local level

The Healthcare Technology Innovation Cycle connects engineers and medical professionals, scientists and entrepreneurs, and developers and end-users (medical doctors and patients) (Figure 1). The concept of an innovation cycle implies a virtuous circle of interaction. The European Alliance for Innovation defines an innovation cycle as representing a framework for classifying the different stages of innovation and the stakeholders related to the development of innovation⁴.

The healthcare innovation cycle contains three stages and numerous stakeholders. The first specifies resources (inputs) (e.g., the science in the research base, research funding, human capital). Central to this is the national context. In the second, the innovation systems most closely resemble that of a sectoral innovation system (SIS) (Malerba 2002, 2005). It includes technology transfer capacity building (e.g., infrastructure and support for technology transfer).

⁴ <http://eai.eu/about-us/innovation-cycle> (accessed February 3 2016).

The third stage includes outcomes (e.g., new firms, jobs, drug developments advances in diagnostics, therapeutic and other technologies) rather than production capabilities and links to customers which are elements in ‘global’ commodity chains, which concern interconnections within and across varied geographical scales (see Birch 2008).

Within each element of the innovation cycle are stakeholders – governments, universities, and various other private sector organisations. However, as it is a cycle, this process is not linear. Feedback loops involving interactions between the different elements (Kline and Rosenberg 1988, Rothwell 1994) contribute to the vitality of individual cycles.

Figure 1 here

A limitation of the healthcare innovation cycle concept is the lack of a sense of place and a broader geography of innovation, which Cooke (2005) and Swiss Biotech (2016) refer to as an “innovation value chain” in the sector. The analytical agenda in this paper is that of a place-based analysis taking into account where key components of internationally organised healthcare innovation value chains are located (i.e., the whole spectrum of innovation from resources to outputs). This approach resonates with different typologies of systems involving interconnections between different geographical scales.

Birch (2017) applies the value chain concept to examine where innovation happens in the life sciences, and considers where and how value circulates, and who captures the value produced. This approach is useful because by implication, the local geographical dimension is where value creation and exploitation takes place. To explore that aspect we draw on research evidence to ‘ground’ the innovation cycle concept.

In the healthcare sector, key inputs are scientific knowledge, research funding, human capital and research infrastructures. Each of these is connected to research universities which are often the central players in geographies of innovation. A key feature of the bioscience sector is national funding for research, whether it is the National Institutes of Health in the US (Breznitz and Anderson 2006), federal/central government agencies in Europe (e.g., Switzerland), the Medical Research Council in the UK or the EU under the Horizon2020 Programme⁵. National is the dominant level of provision of resources for the production of scientific knowledge (e.g., research funding, infrastructure, the education and training of human capital) investing in scientific frontiers (Mazzacato 2013), as well as determining other property rights to knowledge important in the bioscience sector⁶. In some, the regional level is the primary source of such resources (e.g. Länder in Germany, Cantons in Switzerland). These regional entities facilitate technology transfer through layers of policy linking national and local levels. Other organisations (e.g., firms, research institutes, hospitals) also provide knowledge and support the infrastructure for innovation, such as science parks and incubators.

The starting point of the HealthTIES project was that the chosen regions each had strong science bases (scientific knowledge) which underpinned the development of the healthcare sector. Coenen et al., (2004) find that the dominant knowledge base of the bioscience sector is connected to the science base as a source of knowledge. The sector is characterised by strong spatial concentration around nodes of excellence, such as in the four HealthTIES regions. These are then themselves interconnected through international networks. Inputs are analytic knowledge while companies use sources of synthetic knowledge such as hospitals, specialised

⁵ <https://ec.europa.eu/programmes/horizon2020/en/h2020-section/nanotechnologies-advanced-materials-advanced-manufacturing-and-processing-and> (accessed November 18 2015)

⁶ <https://www.bio.org/intellectual-property> (accessed February 16 2017)

services, suppliers and customers for testing, (re-) designing, or commercialising new discoveries and inventions. Knowledge combinations are relevant in both cases.

Different mixes are found in biotech generally in technologies, inputs and demand (Todtling and Trippel, 2015). Moreover, not all local analytical knowledge bases are the same in healthcare as in the specific case of biotech because of different levels of research funding priorities, specialisations, engagement in research consortia and so on. In addition, synthetic knowledge where innovation takes place mainly through the application of existing knowledge or through the new combination of existing knowledge for example in public-private partnerships, is also a key element of healthcare innovation value chains. These varieties of innovation pathways are key to understanding our cases.

Implicit in this cycle schema embedded in the concept of resources (inputs) is the idea that there are a variety of knowledge transfer mechanisms in place in a locality. One example is the interaction between individuals and organisations in clusters in spreading knowledge and expertise, while keeping the process spatially bound (Breschi and Lissoni 2001). Birch (2008, 87) in a critique of cluster approaches cites Malmberg (2003), Malmberg and Power (2005) and Malmberg and Maskell (2006) stating that, ‘it is important to explore both the concentration *and* dispersal of innovation across multiple scales’. This point is reinforced by Moodysson and Olsen (2007) who also find that while functional proximity facilitates technology transfer, global knowledge collaboration is indispensable for most dedicated biotech firms. This raises the issue of which actors and under what circumstances local collaborations are important.

A further category of resources in healthcare is high skill human capital. This is particularly associated with innovation-led entrepreneurial activity (Audretsch and Keilbach 2005), with

entrepreneurs being drivers of innovation. Fritsch and Wyrich (2014) argue that where there are concentrations of the highly-skilled, this is often related to a high quality science base. A local environment includes other skill sets including those of intermediaries (Howells 2006) including technology transfer officials who mediate in the technology transfer process, for example by supporting the formation of new firms or connecting the researchers to the next stage in the cycle, that of innovation systems.

Basic to the innovation cycle in Figure 1 is the capacity in the second stage for sustaining the development of the local elements in the internationally organised innovation system. The systems literature includes an increasing number of types of system which comprise a broader framework of innovation geographies. In general the systems concept embraces stakeholders, public and private sector actors, and the networks which link them (see for example Woolthuis et al. 2005, Coenen et al., 2006). These include national innovation systems (NIS) (e.g. Freeman 1995, Lundvall 1988 & 1992, Nelson 1993), regional innovation systems (RIS) (Cooke 1992), sectoral systems of innovation (Malerba 2002, 2005) and varieties of business ecosystems e.g. entrepreneurial ecosystems (Spigel 2015).

The healthcare sector as it appears in the innovation cycle has some elements of a sectoral system of innovation (SIS) but is not confined to one product group. Breschi and Malerba, 1997, 131, in Coenen et al., 2006) define an SIS as “a system (group) of firms active in developing and making a sector’s products and in generating and utilizing a sector’s technologies”. Coenen et al., (2006) suggest that the boundaries of an SIS are defined by a certain product group with a dominant knowledge base.

In the SIS concept, policy makers (central government and local authorities) appear as agents of change in the system alongside firms and non-firm organizations (such as universities or

financial institutions), as well as organizations at lower (R&D department) or higher level of aggregation (e.g., firms' consortia) and individuals (Malerba 2002). The absence of formal administrative boundaries in the concept is relevant to the healthcare sector analysis as although we discuss evidence of activity at the local level, the overall context is that of an internationally organised field (see Coenen et al., 2004).

While the RIS approach does recognise interconnections at various spatial scales, it is essentially a territorially bounded system (Coenen et al., 2006) but with extra-local linkages. Asheim and Coenen (2005, 1174) define RIS as “interacting knowledge generation and exploitation subsystems linked to global, national and other regional systems” that may stretch across several sectors in the regional economy. The capacity of the constituents of a regional economy allows for the support of science and technology discoveries and their application for example through networks between local stakeholders (e.g., entrepreneurs, intermediaries) and infrastructure e.g. science parks (Casper 2013).

However, a weakness in the HealthTIES innovation cycle, as in other innovation systems approaches, is that entrepreneurs and enterprises appear in the system and outputs stages of this cycle, rather than in inputs as actors with agency at the local level (Feldman and Francis 2006, Autio et al. 2014) (see also Sternberg and Muller 2005 on RIS). Feldman (2014) describes entrepreneurs as a missing element in the discussion of innovative places while Hekkert (et al., 2007, 421) argue, “Entrepreneurs are essential for a well functioning innovation system”. Indeed, entrepreneurial activities, together with knowledge development, knowledge diffusion through networks, and market formation, are among the key elements of innovation systems. While university spin-offs appear in innovation systems, only a few such companies are in biosciences and many of them remain small. It is often non-university biosciences spin-offs that are more active players in innovation systems (see Cooke 2005).

System approaches neglect how universities and research establishments change in response to changes in technology, markets, public policy etc. In countries such as those in the HealthTIES consortium, incentives are put in place to create synergies between various research organisations, firms and individuals. Many have resulted in public-private partnerships designed to exploit commercial opportunities. However, these do not occur at the same rate or in the same form in our four locations.

The need for such critical analysis is made by Carlsson et al. (1999) who asked:

- what is the appropriate level of analysis?
- how is a system delineated and which actors form the components?
- what are the key relationships that need to be captured so that the important interaction takes place within the system rather than outside it?

Following from this, further questions arise: how is the performance of the system to be measured? Is this measurement to be at system level rather than at the component level in this case at the regional level? Analysis here takes each element of the innovation cycle in turn.

In summary, the review of innovation systems provides various frameworks to work in evaluating the structure and outcome in different locations. The definition of location, sector, and technology is critical but not simple in the healthcare sector. By nature, this field is not bounded – collaborations often transcend local geographic boundaries, firm boundaries etc. The field is also dependent on multiple disciplines and technologies including non-science areas such as law, public health, social science and management. Studying this complexity requires rich datasets; often studies focus on one technology (e.g. rDNA), one

drug (e.g. Herceptin), one discipline/process (e.g. molecular biology), one firm (e.g. Genentech) and one university (e.g. Stanford).

This paper is an ambitious endeavour to reflect on local regional competitiveness and shortcomings to understand how leading centres in Europe stack up with regards to our understanding of inputs, systems, and outputs in the healthcare sector. Direct comparisons are not possible given the population size of each country and history. However, specializations of each and common threads that cut across these regions can be noted. These observations imply significant possibilities for policy from organizational, local to regional level in order to target synergies.

3. Study context: the four European regions

The US is and has been the leader in translational research in the healthcare sector (Kenney 1986a, 1986b, Bagchi-Sen et al. 2004). In Europe such work is noticed in the UK, Germany (see for example Cooke 2004, 2013), and Switzerland (Gebhardt 2015). Other countries (e.g., Israel, India) have strong science bases but are yet to deliver effective support for this process (Breznitz 2013). Here we consider the national and regional (local) policy contexts in the four European regions.

The four key bioscience regions of the ‘Healthcare Technology Innovation cycle’: Biocat, Medical Delta (MD) Oxfordshire and the Thames Valley (OTV) and Life Science Zurich (LSZ) are what Cooke (2004) has described as bioscience megacentres, albeit on a smaller scale than ones in the US (such as Boston or San Francisco). Their locations are shown in Figure 2.

Figure 2 here.

Three are similar in population size. In 2010-11, Oxfordshire and the Thames Valley (OTV) had a population of 1.1 million, Biocat (Barcelona municipality) 1.6 million; LSZ canton of Zurich 2010) 1.6 million, and MD, the Zuid-Holland region (2011) 3.5 million⁷. MD includes three urban centres (Rotterdam, Leiden and Delft), each with a major hospital. Although a weakness of the HealthTIES methodology is that it is not corrected for population size, in our analysis we do in part use to some indicators factored by population size.

The strengths of the science bases and for translational research are shown in Appendix A. This shows the main research institutes in each, confirming the rationale for comparison even though the evidence collected after the regions were chosen suggests that in some respects they represent different positions in more global innovation/value chains (Cooke 2004, Birch 2008). MD, OTV and LSZ have their research integrated with hospitals so it is difficult to separate out institutes. The Barcelona list is more truly one of research institutes as they are less integrated in the region.

MD and LSZ have regional structures created to promote translational medicine and are most obviously where the whole innovation cycle is organised at the regional level. In both, universities work with private sector engagement as a main driving force in economic development. However, while universities are funded regionally by Switzerland's cantons, they are nationally funded in the Netherlands. They differ in the availability and type of resources, in the key elements of innovation cycles, and as a result, in outputs. They are also

⁷ <https://www.citypopulation.de/> accessed February 9 2017)

dissimilar in the extent to which national governments set sectoral innovation agenda and incentives.

OTV and Biocat have clusters of commercial activities which have grown around their major universities and hospitals. Examples of major national and regional policy initiatives are shown in Table 1.

Spain

Spain has one of the ‘world’s leading centres of biotechnology research’ but lags behind in its technology transfer system and creation of new firms (Wharton 2014)⁸. Research in the life sciences is funded through the Spanish Research Council⁹, which is one of the largest in Europe. Biology and biomedicine are one of eight target areas. It has commercialisation, transfer of results to the corporate sector, and creation of technology-base companies as three of its main functions. While it has had a robust science base, there is evidence that it lacks interactions between different organisations.

In 2014, Spain adopted the Israel model for designing an entrepreneurial and business model based on innovation. The country had been losing its position in the world rankings of research and development activity. The sector had been especially hurt by cuts in public subsidies and the shortage of tax incentives for research, which translate for example into fewer patent registrations. Comparatively weak policy efforts to incentivise knowledge and technology transfer compared to incentives to foster research have further hindered progress.

⁸ <http://knowledge.wharton.upenn.edu/article/spain-adopts-israel-model-engineer-biotech-resurgence/> (accessed March 19 2017)

⁹ <http://www.csic.es/> (accessed February 24 2017)

Spending on R&D (over half by firms) is concentrated in three main centres – Madrid, Catalonia and the Basque country, with Catalonia being one of the country’s national biotechnology hubs, with 20% of all companies in the sector¹⁰.

In Catalonia, the Programme for the Health and Life Sciences Industries¹¹ is one of Seven Strategic Industrial Sectors, published by the Government of Catalonia. Not explicit in Switzerland or the Netherlands, but increasingly the case in the UK, the strategy sees a key role for the hospital sector driving innovation in pharmaceutical and medical technologies. At the regional level, Biocat is the main organiser of the life science innovation cycle. Biocat was established in 2006 by the Government of Catalonia and Barcelona City Council. Its aim was to facilitate networking among biotech and pharma companies, research institutions/universities and an administration that fosters the biotechnological and biomedical sector in Catalonia¹². Biocat is led by a biomedical network that monitors what is happening in the sector, but has more resources and works closely with universities and hospitals. Start-up finance is available through ESBAN, an association of business angels.

The Netherlands

Science policy in the Netherlands has an increasingly close relationship with innovation policy. The government has ‘actively supported and co-funded a research and development infrastructure based on the concept of open innovation and long-term public–private partnerships’ while investing in the strong research base^{13 14}. These partnerships cover the

¹⁰ <http://www.biocat.cat/en/bioregion-facts-figures> (accessed September 30 2015)

¹¹ http://www.catalonia.com/en/binaris/Plans%20Implus_en_tcm213-213851.pdf (accessed February 16 2017)

¹² <http://www.biocat.cat/en> (accessed December 9 2014)

¹³ <http://www.ibnetherlands.org/> (accessed November 26 2014)

entire life sciences value chain: they range from basic research to product and business creation. In cases where they address human health, they reach all the way from bench to bedside. They include all Dutch university medical centres, together with their associated universities.

Medical Delta was established in 2006 by the Delft University of Technology (TU Delft), Erasmus Medical Centre, Erasmus University, Leiden University and Leiden University Medical Center, and the City councils of Delft, Leiden and Rotterdam. MD is coordinated through its website¹⁵. Its aims were to realize breakthroughs in medical sciences and healthcare, to develop novel technologies, and to fuel related economic opportunities through university-industry linkages. MD is a medical technology cluster, home to a large number of biotech firms with stakeholders such as companies, business parks and local government.

The United Kingdom

The UK's strength in life sciences lies in it having "4 of the top 10 universities in the world, 19 of the top 100 universities, a stable of quality service providers, world class charitable supporters of the industry and a rich heritage of globally recognized medical research"¹⁶. The country has one of the strongest biotech industries in Europe. It has strategic approach to life sciences similar to that of the Netherlands. There is a complex policy structure for funding involving research and innovation in universities, research centres and increasingly hospitals. The UK government's 2011 Strategy for UK Life Sciences supports companies through every

¹⁴ <http://www.hollandtrade.com/sector-information/life-sciences/netherlands.pdf> (accessed September 30 2015)

¹⁵ <http://www.medicaldelta.nl/> (accessed December 9 2014)

¹⁶ <http://www.bioindustry.org/home/> (accessed November 26 2014)

stage of the product life cycle. It highlighted weaknesses in the UK healthcare innovation cycle for R&D funding for translational activities or the “translational funding gap”¹⁷ in 2014¹⁸. The Office for Life Sciences (OLS) is part of the Department of Health and the Department for Business, Energy & Industrial Strategy, ‘champions research, innovation and the use of technology to transform health and care service’¹⁹. The regional level has been abandoned as an organising authority in England with Local Enterprise Partnerships (LEPs) now responsible for sector specific policy intervention (if any) (Lawton Smith et al., 2015).

All areas have activity in the medical technology, medical biotechnology, industrial biotechnology and pharmaceutical sectors but the South East (Thames Valley, Oxfordshire), the East of England (Cambridgeshire) and London together contain 60% of all employment²⁰. In OTV Oxford and particularly Oxford University dominates. Its translational trajectory is predicated on its very strong science base much of which is funded by national and international research funding bodies (research councils, national charities and currently the EU). The main local sector network is OBN²¹, a membership organization with some 400 member companies, which has spread its activities beyond Oxfordshire, providing networking, partnership, purchasing and training activities. OBN in practice is not a formal part of a locally organized innovation cycle as is the case with Biocat.

¹⁷ <https://www.gov.uk/government/organisations/office-for-life-sciences> (accessed June 7 2014)

¹⁸ https://united-kingdom.taylorwessing.com/synapse/ti_strategylifesciences.html (accessed February 9 2017)

¹⁹ <https://www.gov.uk/government/organisations/office-for-life-sciences> (accessed February 24 2017)

²⁰ https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/298819/bis-14-p90-strength-opportunity-2013.pdf (accessed May 23 2014).

²¹ <http://www.obn.org.uk/>

Switzerland

Switzerland operates ‘a systemic approach to research’²². As an established approach in Swiss politics, the division of tasks between the private and the public sector in the field of research and innovation is based on two pillars: the principle of subsidiarity and a liberal economy. Thus, the government becomes only active in areas where it is constitutionally authorised so to do. Under the Research and Innovation Promotion Act (RIPA), the Swiss government is responsible for providing grant funding for research and innovation through the Swiss National Science Foundation (SNSF) and the Commission for Technology and Innovation (CTI)²³. The Federal budget through the SNSF and programmes such as the national centres of Competence in Research (NCCR) for university-based education, research and innovation, is very high.

At the regional level, Swiss cantons also fund universities and especially universities of applied sciences (Gebhardt 2015). Gebhardt argues that it is not necessary to use innovation policies as developmental measures in Switzerland since private investment is the key driving force. In the pharmaceutical sector, Switzerland, is now leveraging that strength for broader biomedical sciences and the creation of its national biotech innovation chain²⁴.

²² <https://www.eycom.ch/en/Publications/20160412-Swiss-Biotech-Report-2016/download> accessed February 16 2017)

²³ <https://www.walderwyss.com/publications/1633.pdf> (accessed February 24 2016)

²⁴ http://www.swissbiotech.org/Php5/aa2/UserFiles/File/pdf/swissbiotechreport/SBR_2014.pdf accessed November 26 2014)

The Zurich life science (LSZ) cluster was established in 2001 by the University of Zurich and the Federal Institute of Technology Zurich (ETHZ), both in the Canton of Zurich²⁵. It aims to establish co-operation networks bringing together academia, industry and the public sector, and to support science education. Approximately 80% of the cluster activities are related to human health. In addition to promoting networking and communication within the universities and with the general public, two new networking platforms, the LSZ Young Scientist Network and the LSZ Business Network, have been initiated.

4. Data, Methodology, and Findings

Each HealthTIES project teams collected standardized regional information on universities, research institutes, universities of applied sciences, intermediate vocational education, publications, care and cure providers, government, industry, technology transfer, science parks and incubators. The data, as at 2012, were then benchmarked for each region using a set of indicators which comprise innovation system parameters and best practices, by an analysis of the scientific strengths of the universities and companies by region, together with a Strengths, Weaknesses/limitations, Opportunities and Threats (SWOT) analysis.

Data in Tables 2, 3 and 4 are designed to show the innovation cycle at each stage: local resources (inputs), innovation system and output indicators²⁶. However, this kind of analysis is fraught with methodological complexities owing to the difficulties in defining what is to be measured and reported indicators of performance (Carlsson et al., 1999).

²⁵ <http://www.lifescience-zurich.uzh.ch/en.html> (accessed February 22 2017)

²⁶ Data are available at <http://vrr.healthties.eu/>(accessed) June 3 2013)

For example, the EU's (2011) Economic Performance Indicators (EPIs) for regional biotechnology are categorised under three dimensions: cluster dynamics, enablers, and outputs²⁷. Cluster dynamics includes the number of jobs created and companies established (including growth and survival rates within the last three years). Cluster enablers are designated as the external environment and include public funds raised, private funds raised; framework conditions; and the number of cluster organisations (cluster management/facilitator). Cluster outputs include revenue from marketed biotech products/technologies; revenue from licensing activities on biotechnology products/technologies, and numbers of newly developed and marketed biotechnology products/technologies.

Other measures of outputs from universities include numbers of university products such as patents, licenses, and collaboration (Lendel 2010) as well as spin-offs. All offer a range of possible sources of innovation which could be absorbed within a local economy.

Measurement by geography and the impact of proximity are important but also problematic. Goldstein (2009) for example measures universities' technology transfer by distance, types of research and kinds of universities. He finds spillovers from basic research to be less localised than those from applied research with spillovers from highly ranked research universities more geographically widespread.

Identifying outputs is problematic as studies do not necessarily agree as to what is an input or an output. Moreover, whether inputs and outputs can be actually identified as being 'regional' is a further complication. For the biotech sector, standard output indicators include founding rates of firms, size (employment, turnover etc), specialization as indicated by new products,

²⁷ <http://ec.europa.eu/research/bioeconomy/pdf/regional-biotech-report.pdf> (accessed May 23 2014)

patents and drugs in development. Collectively these shape the specialization of a region from the private sector and universities (BIS 2013).

In keeping with the suggested metrics above, the HealthTIES project developed a set of innovation indicators which were grouped into the three innovation phases: Resources (Input), Innovation System and Outputs²⁸. Data were collected by teams from each of the partners. In Oxford, MD and Zurich, the teams comprised academics working with local organizations. In Biocat, data were collected by the Biocat team. The criteria adopted for the study across the regions for innovation indicator datasets were that the data should be relevant to the HealthTIES disciplines - biotech, medtech, life sciences, engineering and medical sciences, and that discriminate between regional performances should be supported. This illustrates that within the healthcare sector a number of disciplines are involved (Todtling and Trippel 2015).

The datasets needed to be quantitative in order to identify the impact of local expertise and conduct regional SWOT analyses. Our focus is on capacity building and exploitation of existing capacity, that is, the system and its existing strengths and opportunities. We accept that there are limitations to the chosen proxy variables, for example a large number of patents are non-performing, and a great many spin-offs do not deliver significant new products based on research (Balas and Elkin 2013). However, these indicators are believed to be the best available.

The regions differ in the scale of activity, both geographically and in component elements of the innovation cycle. In turn these have reinforcing effects and implications for pathways of development because they influence what future developments are possible. Key

²⁸ The innovation indicators, their weighting and scaling were derived as part of the HealthTIES project.

organizational differences lie in whether the regions exist as virtual, functional or administratively defined regions, in the lead organizations and major players, in the composition of the resource, systemic elements of the cycle, and thence in the scale of outputs, and in relation to the size of population and resources. In the analysis we examine where each region occupies different positions in international innovation/value chains, identifying place based-issues.

4.1 Existing resources, strengths, and opportunities

The differences between each region at Stage 1 of the innovation cycle are illustrated in Table 2. The four regions are specialized in different areas of research and commercialization activities. For example, OTV is a leading region regarding its research activities and capabilities in the health related research sectors and lags in commercialization. An indicator of the region's strength in knowledge is the number of professors with an H-index of 30 and above²⁹. MD, OTV and LSZ have at least a hundred more than Biocat. Per number of professors, however, Biocat has a higher rate of publications (6.4) than MD (4.8) and LSZ (5.2). Oxford's professors' publication rates far exceed all of these (9.5). Other European countries do not yet have an equivalent of the Research Excellence Framework (REF). This is a system for assessing the quality of research in higher education institutions on their research outputs, research environment and impact. It strongly drives academics to publish and obtain research funding. Impact relates 'an effect on, change or benefit to the economy, society,

²⁹ The H-index is a measure which combines publication output and impact through the number of citations of an academic paper, such that a threshold of 30 will identify academics who have published at least 30 papers that have each been cited at least 30 times. H-index increases with length of career, for example a senior, international academic could have an H-index of around 80+, but younger, very productive researchers will also be identified using this threshold

culture, public policy or services, health, the environment or quality of life, beyond academia’

³⁰. Academics can also apply for grants to encourage knowledge exchange.

Oxford University’s academics have had a primary focus on publishing in top journals in order to maintain global reputation. Rather than this being associated negatively with commercialization, perhaps peer-reviewed publications are an important means through which dissemination to industry takes place. Grimshaw et al., (2012) (in Balas and Elkin 2013) argue that most clinical research arises through scientific reviews that synthesize knowledge for practical implementation. It is therefore possible that UK government policy on the REF is supporting key future elements of the healthcare innovation system, as well as in specific knowledge transfer initiatives in life sciences.

Table 2 here

On overall levels of external research funding, LSZ is ahead of OTV. OTV matches that region in the number of ERC junior research grants but lags behind in the number of senior ERC grants. This might indicate that the innovation cycle in OTV is at a comparatively early stage and is focused more on science than translational medicine when compared with LSZ. However, the strength of the research base overall illustrates the primary UK position held by Oxford University and its teaching and medical research functions in local National Health Service hospitals³¹.

³⁰ <http://www.hefce.ac.uk/rsrch/REFimpact/> (accessed February 26 2017)

³¹ <http://www.ouh.nhs.uk/default.aspx> (accessed 30 September 2015)

MD, LSZ and Biocat outperform OTV in human capital particularly in the ability to attract more overseas as well as national MSc/PhD students. LSZ has more international PhD students and graduated MSc students, both national and international, suggesting that it has a younger profile than the other regions. However, it is Biocat that has by far the most PhD students and OTV has by far the least. Taken together, per head of population Biocat has the highest percentage 0.7%, next is LSZ, 0.4%, followed by, Oxford 0.13% and MD 0.1%. This is an indicator that the regional environment (Casper 2013) in OTV and MD is less favourable. This suggests that the local labour market might be attractive to local and inward investors whereas a lack of skilled professionals in OTV and MD might be bottlenecks for a growing industry.

Biocat is the strongest region for translational medicine overall with respect to the number of both research and general hospital beds in its much higher number of hospitals, and in the number of clinical trials for its population size (0.3%). This with its smaller number of professors with high H-indexes, lower levels of publications, research income and much smaller research infrastructure indicates that its position in an internationally organised healthcare innovation value chain is that of teaching and applied research. There are potentially greater opportunities for stakeholder engagement and agency at the local level to develop translational research activities given the high level of regional funding.

In contrast, the small number of research hospital beds at OTV might hamper the development of advances achieved through the interaction between research and patients, thus limiting experimental capacities. This is in spite of institutional capacity in the form of a regional clinical trials consortium.

4.2 Innovation Systems

In Stage 2 of the innovation cycle, one of the main differences in the respective innovation systems relate to the size of the physical infrastructure (Table 3). Biocat far outperforms the other regions in the space provided in its science parks and has stronger institutional capacities in the form of a vastly high number of technology transfer officers both in the science parks and in the universities.

However, this does not translate into significant differences in the numerical value of commercialisation in an innovation value chain in the form of the number of spin-off companies. Biocat does have the most spin-offs, nearly double the number in OTV and LSZ, but not that many more than MD. The greater number might mean that the agency of entrepreneurs in creating institutions and building capacity (Feldman 2014) is stronger than in the others. It is the case therefore that entrepreneurship is necessary for innovation in the healthcare sector, but this study also illustrates that this is not sufficient to drive forward innovation, whereas the state is necessary but not sufficient by itself and needs other system elements to interact.

Biocat's place in an international healthcare innovation value chain differs from that in MD and OTV particularly. MD and OTV have the most big public-private partnerships, which are internationally organised (Birch 2008). What is seen here is a hybrid domain of important technology advances – a combination of analytic and synthetic knowledge (Coenen et al., 2004). However, the number of granted US patents of potential value realisation tells a different story, as there is a fairly uniform number across three regions, with LSZ having fewer.

OTV has the second largest provision of space but its infrastructure for incubation of new and growing biotech firms is weak. SQW (2013) also identified a lack of available premises inhibiting the location of Big Pharma and a lack of linkages between Oxford University and local firms. Oxford University has now started building the Bioescalator (an incubator) amongst other research institutes, next to the Churchill Hospital. This eventually will be ‘a hub for the commercialisation of bioscience and medical research and innovation in Oxford’³². Three other bioincubators are planned in Oxfordshire³³.

Where the evidence is lacking is on local inter-linkages which the cluster literature suggests are drivers of innovation (but see Malmberg and Power 2008, Birch 2008) and central contributors to innovation. The evidence suggests that local intervention is important. Specifically organised innovation systems can produce better performance.

4.3 Outputs

One of the major differences is in value realized by commercial activity or outputs in the regions if employment is taken as a proxy (Table 4). LSZ dominates the number of larger biotech companies which is over twice those of MD, while Biocat and OTV are way behind. LSZ also has many more jobs than two of the other three in the smaller biotech companies. Biocat comes close to LSZ in jobs, mainly employed in its smaller firms.

³² <https://www.medsci.ox.ac.uk/newsletters/may-2015/innovation-initiatives-resources/innovation-initiatives-and-resources/the-oxford-bioescalator> (accessed February 24 2017)

³³

http://www.oxfordmail.co.uk/news/10969638.67m_investment_into_four_science_hubs_in_Oxfordshire_firms_main_part_of_three_part_Oxford_City_Deal_Audio/?ref=var_0 (accessed December 9 2014)

In spite of OTV's strong research base, its ability to commercialise research seems to be limited. Employment in the biotech sector is half that of Biocat and somewhat over a third that of LSZ. Its poor performance might indicate that despite the very strong scientific labour market, which is associated with high levels of entrepreneurship (Fritsch and Schindele 2011), the area appears to lack people and capabilities for supporting commercialization or fostering entrepreneurship, which seem to be present in all the others. This is consistent with the finding that OTV has a weaker regional environment (Casper 2013). This could also be related to the lack of a local interventionist policy for the sector. This may be a short-term problem: OTV was able to attract throughout Europe the largest amount of investments between 2007 and 2010 with 420.75 million Euro (followed by MD with 215.38). This indicates a perceived (scientific/economic) potential for further growth by investors and this has the potential to increase the output of the region over time.

Another prime indicator of commercialization is in the number of products on the market. Here LSZ scores most highly, followed by Biocat. This suggests that in Switzerland it is the private sector that is driving developments, a characteristic of the national innovation system, while in Biocat a government policy of collaboration is having an impact. However, OTV has the highest number of products in clinical trials, but is third highest in products at the discovery stage. This shows that there are no clear cut patterns to translational research across the board, rather there are indicators of where different kinds of agency are being felt in producing outcomes.

Table 4 here

What the data in the three tables cannot show are direct outcomes in innovative healthcare. Other indicators such as new therapy and health care structures, efficacy and effectiveness

indexes could be more appropriately constructed as outcome indicators. These indicators would be a first step in identifying national, regional and local conditions that underpin potential advances in healthcare and hence can be used to identify appropriate policy responses.

5. Conclusions

In this paper, the concept of an innovation cycle has been used to examine the healthcare sector in four leading regions in Europe. Data collected at one point in time are used to reflect on our main research question: how has the innovation cycle in the healthcare sector developed in each of the four regions? A related question is also examined: what does the elements of innovation cycles tell us about the location of value in international value chains? This question is asked in economic development and policy cycles given the importance of local-international networks for innovation.

To answer our question, we use data from HealthTIES supplemented with discussion on the place-specific contexts within which the data are meant to be analysed. From this analysis the development paths can be seen and comparisons across places made to show the relative positioning of the regions within internationally organised innovation value chains. Moreover, this sector provides both economic and social benefits. Past studies recognize that a thriving innovation oriented healthcare sector is seldom inward looking, collaborations abound. Although comprehensive data on collaboration across value chains do not exist, capacity data are available to some extent for parts of the value chain in different regions.

Data on the three stages of the innovation cycle, (resources/inputs, systems, and outputs) give information on those differences. The resources tell us about capacities, the innovation system tells us about interactions, and the outputs provide indicators of the effectiveness of commercialisation process in each. Although we do not have time series data, we can use the cross-sectional data to show the outcome of investment, utilisation of resources, and provide implications for broader impact through a presentation of policy needs and data needs.

We show that with respect to resources, the four regions are specialized in different areas of the innovation cycle. OTV is clearly an outlier being dominated by analytic rather than synthetic knowledge (Coenen et al 2004) but not in all respects, particularly in human capital. While MD and LSZ are similar to OTV in the number of research professors, this does not translate into the same level of publications. All three other regions have far higher student numbers than OTV, both at Masters and PhD levels. Three regions, (but not OTV), are converging in the inputs to support commercialization. OTV lags behind the others, especially behind Biocat, in the number of hospital beds and clinical trials, which represent later stages of the innovation process.

Biocat, however, is well behind the others in the availability of university infrastructure for research. LSZ is well ahead of the others with respect to research funding and associated university research areas for research. We note how public policy and private sector involvement have produced distinctive characteristics either through enabling or not enabling processes needed for translational research.

In ‘innovation systems’, Biocat is the leader particularly for physical infrastructure, especially in the number of full time TTO employees. It has more university spin-offs than the others but there is an imbalance between the resources devoted to commercialisation and the

resulting extent (spin-offs and patents). Similarly the evidence suggests that OTV's TTO resources are relatively inefficient as they have not resulted in as many university spin-offs pro rata. A strength of MD's innovation system is in the number of big public-private projects that have an applied, commercialization element (synthetic knowledge, Coenen et al. 2004).

The evidence suggests that it is in systemic features where MD, LSZ and Biocat are converging, but not necessarily through the same kinds of public policy intervention (Table 1). Where Oxfordshire's LEP celebrates the strength of the life sciences research base, its policy priorities are more to do with creating a favourable environment with strategic interventions linked to infrastructure. It is considerably behind LSZ and Biocat in commercialization of research over a wide range of resources, innovation system and output indicators.

OTV is an outlier in other ways. It lacks the range of infrastructural support that is present in other regions such as incubators and technology transfer support. It has a comparatively low number of young academics graduating but has a high capacity to import. A serious weakness is its apparent low capability to create spin-offs and to profit from its strong research as well as patent base. This might indicate insufficient capabilities regarding the commercialization process as well as insufficient entrepreneurial education.

It is 'outputs' where there is most obvious evidence of divergence across a range of indicators, indicating that the trajectories of the region in translational medicine are different. This is particularly the case with respect to the roles of entrepreneurs in driving innovation systems rather than being merely outputs. MD is the leading region in the number of companies but less so in the number of larger companies (those with more than 20 employees). Hence there are limitations to its overall sectoral innovation system (Malerba

2002, 2005). LSZ is the most efficient in generating the largest number of successful firms, as is also indicated by the number of products on the market. OTV again diverges from the other three regions in translational activity in the number of biotech companies at all sizes.

However, OTV has the highest number of products in clinical trials and total investments indicating its specialist position in the healthcare innovation chain, that of a developer of potential innovations.

In our case, holistic analysis does not provide answers of who is doing what to achieve better results. What these frameworks do tell us is what data we need. Furthermore the organization of the healthcare sector in each region is different and the national contexts are dissimilar so data really are often non-comparable and somewhat unreliable. At the same time the absolute values (not per capita) tell us about potential policy agenda.

We have used the concepts of innovation cycle for the framework of analysis. This has also drawn on SIS and innovation value systems rather than with boundaries (NIS and RIS), to better analyse our cycle. It sets out elements that at different stages in innovation processes produce outcomes in a circle of interaction. In principle this circle is virtuous but where key elements at each stage are lacking, opportunities for certain pathways of development are limited.

An implication for policy is that as nations move toward knowledge-based economic development, universities are a necessary but not sufficient condition for scientific research to create profitable and socially valuable innovations. There is scope for public policy to identify how the local infrastructure might be improved and hence feed into stronger internationally organised innovation systems. The strength of the science base does not necessarily result in new firms and applied projects, even though a normative policy agenda might suggest that it

should. However, downplaying scientific publications could underestimate their importance in innovation value chains. As Balas and Elkin (2013) suggest, better understanding is needed on the scientific publication pathway in innovation success.

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	Recent national innovation measures	Regional public sector interventions
Spain	<p>Center for the Development of Technology and Investment (CDTI) established a fund that aims to direct 1.2 billion euros into the sector through the Official Credit Institute (2014).</p> <p>No specific tax incentives for biotech SMEs, other than general research and development (R&D) incentives.</p>	<p>Catalonia Programme for the Health and Life Sciences Industries Strategy (2014) includes development of own products by companies with a view to establishing processes of internationalization.</p> <p>Barcelona Clinical Trials Platform (BCTP), a strategic instrument promoted by the Catalan Health Department at the Government of Catalonia and Biocat to improve the coordination, integration, quality, and speed of clinical trials in the region³⁴.</p>
Netherlands	<p>The Netherlands innovation policy focuses on nine priority sectors — one of which is life sciences and health. The Government established the organization Topsector Life Sciences & Health³⁵.</p>	<p>Medical Delta</p>
UK	<p>2009 Academic Health Science centres (AHSCs) focused on how the national health service (NHS) identifies, develops and adopts new technologies</p> <p>2013 Academic Health Science Networks (AHSN, 15 AHSNs across England, established by NHS England to spread innovation at pace and scale – improving health and generating economic growth</p> <p>National Institute for Health Research (NIHR) funded 11 Biomedical Research Centres (BRCs).</p> <p>2012 Cell therapy catapult</p>	<p>Local infrastructure project - Oxford University BioEscalator (entrepreneurship incubator on hospital site)</p> <p>Oxford AHSN</p>

³⁴ <http://catalonia.com/en/trade-with-catalonia/life-sciences.jsp> (accessed February 24 2017)

³⁵ [http://www.ey.com/Publication/vwLUAssets/EY-biotechnology-in-europe-cover/\\$FILE/EY-biotechnology-in-europe.pdf](http://www.ey.com/Publication/vwLUAssets/EY-biotechnology-in-europe-cover/$FILE/EY-biotechnology-in-europe.pdf) (accessed February 22nd 2017)

<p>Switzerland</p>	<p>National Research Programs (NRP) are commissioned by the Swiss Federal Council to deliver solutions to stakeholders in the national and cantonal governments e.g. on antimicrobial resistance.</p> <p>National Centres of Competence in Research (NCCR) the SNSF provides another tool to strengthen research of strategic importance for the future of Swiss science, business and society. Centres help to establish a network of collaborations and partnerships between the universities and the private sector; maintaining links to potential users of research results ³⁶.</p>	<p>LSZ Wyss Zurich (2016) is a multidisciplinary translational science center at the University of Zurich and ETH Zurich. It bridges the gap between the generation of an idea and the translation of this idea into commercial applications, e.g. through spin-offs, out-licensing deals and trade sales³⁷.</p>
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Table 1 recent policy initiatives in each country and region

³⁶ https://www.swissbiotech.org/sites/swissbiotech.org/files/webmasterfiles/swissbiotechreport/sbr_2016_web.pdf (accessed February 22 2017)

³⁷ <http://www.wysshzurich.uzh.ch/>

Category	Parameter	Biocat	Medical Delta	Oxford & Thames Valley	Life Science Zürich
Knowledge	Professors with an H-index >30	125	245	238	231
	Publications 2001-10	798	1171	2264	1190
Research funding	Research Funding (Euro)	450.69	463.23	632.99	1042.09
Human Capital	International current PhD students	1384	843	345	2762
	National current PhD students	3742	1367	805	2167
	Junior European Research Council grants 2007-10	5	4	16	17
	Senior European Research Council grants 2008-10	6	9	19	33
Infrastructure	University area for research (m ²)	1147	77545	193353	315000
	Beds in research hospitals	5908	2096	1043	3366
	Clinical trials phase I & II	120	45	40	36

Table 2: Inputs Indicators

Source: <http://vrr.healthties.eu>

Category	Parameter	Biocat	Medical Delta	Oxford & Thames Valley	Life Science Zürich
Innovation	University Spin-Offs 2007-10	63	50	36	33
	Granted US patents 2007-10	50	54	50	40
	Big public-private projects	29	69	59	41
Support	TTO Full-time equivalents	245	62.9	89	37.6
	Science parks area (m ²)	438920	1007500	312528	88700
	Science parks support Full-time equivalents	181	22	49	17.75

Table 3: Innovation System Indicators

Source: <http://vrr.healthties.eu>

Category	Parameter	Biocat	Medical Delta	Oxford & Thames Valley	Life Science Zürich
Jobs	Biotech companies Full-time equivalents	29981	18636	13563	34440
Companies	Biotech companies with <20 Full-time equivalents	338	195	154	1449
	Biotech Companies with >20 Full-time equivalents	16	108	46	262
Deals	Big Trade Sales 2001-10 (>100 mio Euro)	4	5	4	2
Products	Products on market	207	138	122	282
	Products clinical trials	35	30	66	43
	Products discovery phase	72	55	49	37
Capital	Total investment 2007-10 (>100 mio Euro)	57.33	215.38	420.75	130.30
	Number investments 2007-10 (>100 mio Euro)	13	11	20	16
	Av. Series A investment 2007-10 (>100 mio Euro)	3.96	9.17	9.10	3.97

Table 4: Output Indicators

Source: <http://vrr.healthties.eu>

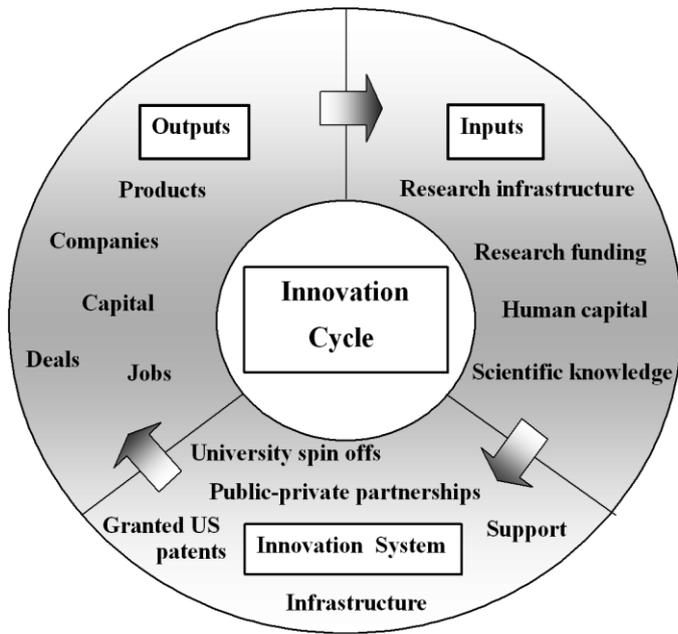


Figure 1. HealthTIES Innovation Cycle

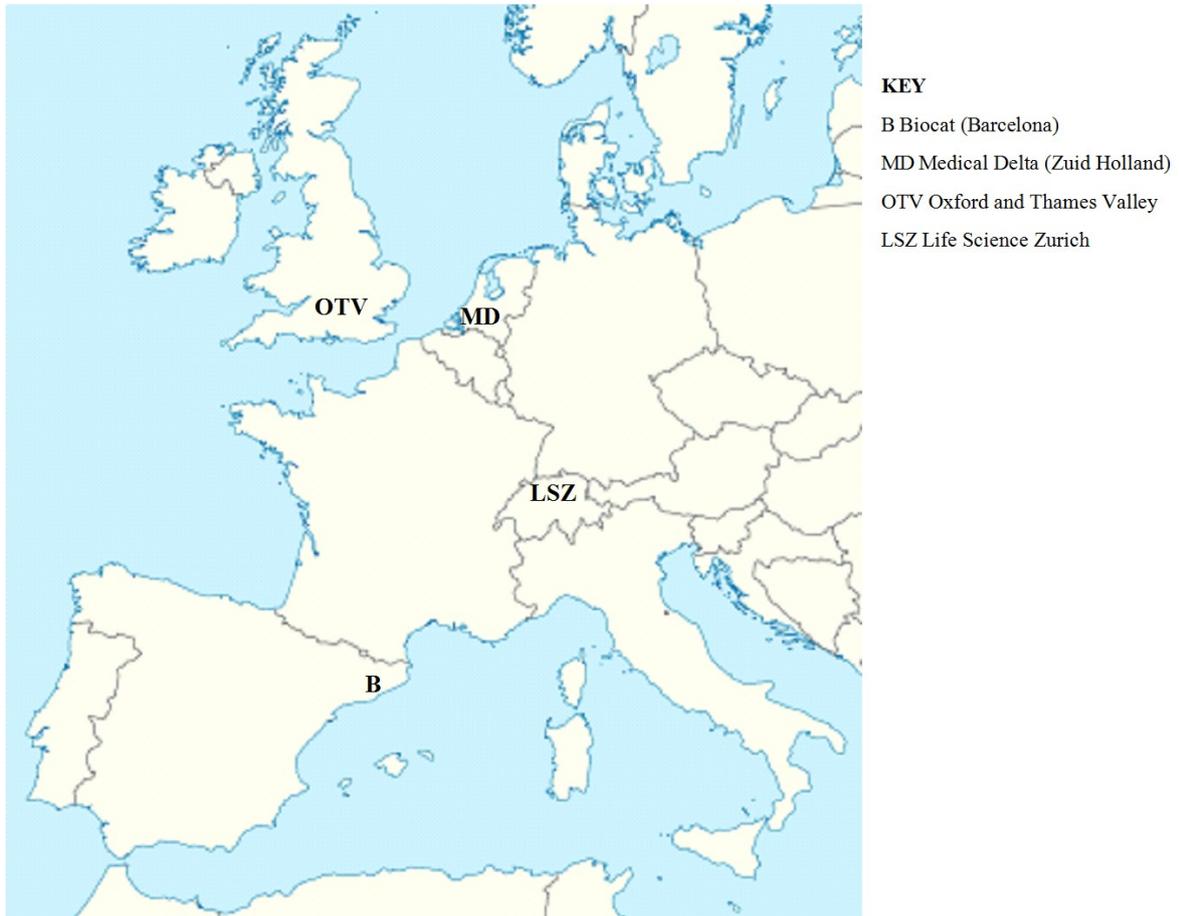


Figure 2 Map of Western Europe showing HeathTIES regions