The effects of patenting on the development of diagnostics products.

How patents influence incremental innovations and monopolies in market niches.

Master Thesis Innovation Sciences

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Summary

In 1998 Heller and Eisenberg raised concerns that patenting of genes could be counter to the common social interest. This sparked extensive research on the effect of gene patenting on research and product development. To date there is a lack of a comprehensive picture of the effects of gene patenting on product development. We operationalize this research gap by analyzing how patents influence market niche based on gene patenting and those based on other biological patents. To test the effects we sampled 288 market niches for diagnostic products approved by the FDA and we linked them to 1199 patents in the USPTO and 1602 licensing agreements. We test whether different qualities of patenting affects the rate of incremental innovation, the strength of monopoly and the strength of the barriers to entry in a market niche. The results show that patenting of genes does not have different effects than other type of patenting, thus the concerns of raised by Heller and Eisenberg on product development remain unsubstantiated.

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Contents

1. Introduction

In 1998 Heller and Eisenberg introduced a theory of Anticommons in Biomedical Research (Heller & Eisenbeg, 1998). This term was used to describe a situation where "multiple owners each have a right to exclude others from a scarce resource and no one has an effective privilege of use" (Heller & Eisenbeg, 1998, pp. 698). They pictured this situation in the biomedical research where the patenting of genes in 1980 was foreseen to have influences on the upstream research and downstream product development. In fact they argued that a repository of genes is a useful tool for discovery, but assigning propriety rights over 'isolated gene fragments' would not be likely to promote societal benefit (Ibid). In their view assigning intellectual propriety (IP) over gene sequences transforms these public resources into scarce resources creating the premises to an "Anticommons Tragedy". Such fragmentation of IP rights over genes was expected to burden the development of gene-based products such as therapeutics and diagnostics, while at the same time limiting the use of other gene based tools in research, thus hampering knowledge production.

This issue is closely related to a market failure exposed by studies in Economies of Science (EoS) (Dasgupta & David, 1994). Such failure regards the production of knowledge, namely free riders capturing most of its benefit and thus restricting the incentives for knowledge production and disclosure (Ibid.). To ensure the disclosure of knowledge, a novel state policy was introduced in 1980 to support knowledge privatization in universities (Nicol & Nielsen, 2003; Pressman, 2012). Academics feared that this would deter timely sharing and access of research results (Blumenthal & Campbell, 1997; Campbell & Clarridge, 2002) and research material (Walsh et al. , 2003; Walsh & Hong, 2003) damaging upstream research. At the same time, this policy would produce concurrent fragments of IP and bring to the formation of patent "thickets" necessary for the production of products (Heller & Eisenbeg, 1998). For example, Heller and Eisenberg (1998) argue that pharmaceutical companies test their drugs on a whole family of receptor to identify the potential therapeutic use. If these receptors are patented by different institutions a thicket of patents needs to be pursued in order to carry out the testing(Heller & Eisenbeg, 1998). The formation of these thickets would delay or prevent the development of tools because of the time and other resources needed to find a common agreement among several actors with different interests. The formation of these thickets would and in also increase the product prices due to the stacking of licensing fees(Heller & Eisenbeg, 1998; Shapiro, 2001).

Although there is fear that privatizing knowledge around DNA has a negative influence on development and supply of products for medical use, so far there is a lack of evidence supporting this claim. Studies on the effects of EoS and the Anticommons Tragedy are extensive on the topic of upstream research[1] (Caulfield et al., 2006; Murray et al.,2008; Nicol & Nielsen, 2003). For example Huang and Murray (2009) studies report evidences that avenues of research where numerous patents are present are less appealing to researchers. Similarly Cohen and Merrill (2003) report researchers tend to avoid the use of patented tools and procedures. On the other hand, downstream development is to some extent overlooked. Studies on the patents granted by universities and governmental institutions observed the effect of different licensing behaviors on product development, finding that licensing activities are common and that exclusive licensing is related to faster product development (Pressman, 2012; Pressman et al., 2006). Studies on product access[2] only consider a handful of cherry picked cases that employed surveys and

[1] These are discussed in depth in the theory section.

[2] The present study considers product access downstream of product development.

interviews of key opinion individuals and provided useful insights for ad-hoc policy measures, but their results are hardly generalizable to the whole downstream product development (Cho et al., 2003; W. Cohen & Merril, 2003; Merz et al., 2002). The claims of Heller and Heisenberg regarding the product landscape remains largely unexplored in the step between patenting and access. Walsh et al. (2003) suggest that perhaps there is no effect. They have surveyed 25 firms, none of which reported a project being stopped because of IP and thus suggesting that DNA patenting does not provide an effective monopoly over a product or process, nor cuts out the competition. Furthermore, they indicate that licensing and inventing around DNA patents are a possible solution when a project confronts intellectual propriety infringement (Walsh et al., 2003).

To address this literature gap we set to evaluate how patents of genetic sequences (also known as DNA patents) influence the development of diagnostic devices in different market niches. Heller and Eisenberg (1998) speculated that patenting would hamper and delay their development, adopting their point of view we compare differences between devices likely to be effected by gene patents and devices not likely to be affected by gene patents. While some technologies use genes as biomarkers[3], others use biomarkers of different nature to provide a diagnosis. Genes are considered difficult to invent around and to be easily used to block competitors (Nicol & Nielsen, 2003; OECD, 2003). For this reason a difference in the level of competition is expected between technologies using genes and those using biomarkers of other nature.

We use product classes (PC) provided by the US Food and Drug Administration (FDA) as a parallel with market niches. Each niche is likely to be subject to differences in knowledge, competition, productivity and speed of product development(Cefis, 2005; Dosi & Nelson, 2009). We investigate the presence of a link between the quality of product supply in the market niche and the patenting practices of the biomarker exploited in the niche. The differences found between PCs based on gene and PCs that use biomarkers of other nature will provide a clear answer to fill the literature gap concerned with the effect of gene patenting on the downstream product development.

To study this issue the following research question is formulated:

How does gene patenting influences the quality of diagnostic products supply?

Therapeutics, engineered tissues, and cultures are also developed on the base of the knowledge embodied by gene patents thus it is expected that findings in the field of diagnostics can be reasonably generalized to the broader landscape of products based on genes (Nicol & Nielsen, 2003; Pressman et al., 2006).

Answering this research question will be of relevance for policy makers and managers. It will shed light on the policy issues concerned with the market failures of the production of public knowledge, its freerides and the policy measures to be undertaken to encourage knowledge production without limiting its use (Dasgupta & David, 1994). The main challenge for policy makers is finding the right balance between incentivizing entrepreneurs, investors and companies to pursue expensive and uncertain R&D activities for product development and ensure knowledge diffusion and exploitation (Pressman, 2012). Fine grained results will point out whether different technologies and knowledge source may need tailored IP policy measures to encourage product development. For managers the nuances in the answer will point out obstacles and aids for obtaining the knowledge needed for product development and provide a

[3] This term is explained in the Setting the stage section

methodological to interpret the chance of success in different market niches. The study will provide insights on which channels best pursue the needed knowledge depending to the characteristics of the market niche under considerations.

In the next section we introduce the product development of diagnostics and its technological foundation. In the theory section we discuss the dependent variable, Economics of Science and Anticommons literature linking it to previous studies of the diagnostic industry and we formulate hypothesis. Then we illustrate the data gathering procedure and the construction of two database considering the same observation at different points in time. In the subsequent section we present the descriptive statistics, data analysis and result of the first database. Then we illustrate descriptive statistics, data analysis and result of the second database. A discussion ends the document.

2. Background

This study focused on products of the in vitro diagnostic industry also known with the acronym IVD. This industry was chosen because of its aggressive practices in defending IP rights (Cohen & Merril, 2003). Most of the companies in biotechnology are in favor of allowing academics to infringe on their patents under a research exemption[4]. However diagnostics are an exception to this common practice. Diagnostic companies fiercely protect their IP also when it is used from research institutes (Cohen & Merril, 2003). This make the IVD industry an extreme case and it makes it an interesting sample for the research. In fact, if no strong effects are found in the IVD industry it is unlikely that any effects take place in any industry.

In each country a governmental agency is responsible for regulating and monitoring the access diagnostic products to the market. The FDA was chosen because of the ease of access to data on the approved products (FDA, 2016d, 2016i; Santos, 2013), and its central role in the commercialization of any product on the US market, which is considered the most profitable, thus attracting the most requests for product approval (Institute, 2011).

Of the whole of diagnostics, this study focuses on in vitro diagnostic (IVD) since most of the DNA based products fall in this category. The term IVD refers to those tests conducted on samples took from the body, such as tissue and biological fluids (The Lewin Group Group, 2005).

The FDA define IVD:

> "[T]hose reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body."
> (US Food and Drug Administration, 2010, 21 CFR 809.3)

2.1 Product development under FDA regulation

Regulation posed by the FDA are a main factor in product development together with competition law and reimbursement scheme (The Lewin Group Group, 2005).

[4] Research exemption is valid for those laboratories that research "solely for amusement, to satisfy idle curiosity, or for strictly philosophical enquiry" (Cohen & Merril, 2003, pp. 13).

The FDA is responsible for the regulation of Diagnostic Devices in the US (FDA, 2016i; The Lewin Group Group, 2005). Diagnostic firms have to be able to navigate the complex regulation requirements posed by the FDA in order to successfully market their products (The Lewin Group, 2005).

The FDA classifies medical devices in three classes according to the degree of risk associated to them: low (class I), medium (class II), or high (class III) (FDA, 2016a). For class I general controls are sufficient. Class II devices require general control and special control, these are submitted through a pathway that goes by the name of Premarket Notification (PMN) or 510 (K). Class III devices go under a Premarket Approval (PMA). A PMA is by comparison more burdensome than a PMN as:

- it always requires clinical data while a PMN requires it only at times,
- it takes 180 days to get a determination against the 90 days of a standard PMN,
- the whole process can take from 6 months to 2 years, during this period the device cannot be marketed.

Thus companies favor a PMN over a PMA when possible.

Products belong to a product class[5], the products in the PC are consistent in the type of technology and nature of biomarker used and can be often linked with a specific medical condition they attempt to address.

2.2 Technological background

2.2.1 What is a biomarker?

IVD technology hinges on biomarkers. As Strimbu and Travel define it "The term "biomarker", a portmanteau of "biological marker", refers to a broad subcategory of medical signs – that is, objective indications of medical state observed from outside the patient – which can be measured accurately and reproducibly." (Strimbu, K., & Tavel, 2010, pp1). The end goal of any diagnostic tools is to identify and measure one or more biomarkers to provide information to healthcare professional. The identification and, at times, quantification of a biomarker is the cornerstone on which the diagnostic device is built.

Technologies for diagnosis are developed at a fast pace and the same biomarker can often be addressed by multiple technologies. Even if the same medical condition manifest several biomarkers (Pressman, 2012), it does not surprise that diagnostic companies strive for patenting biomarkers.

It is intuitive that patenting of a biomarker assigns the owner a competitive advantage over the competitors. Aim of this research is to reveal if the downsides of the patenting practice outscore its benefits and whether there is a substantial difference between the patenting of genes and other biological material.

2.2.2 Technological classification

To capture the effect of patents on diagnostic an accurate classification of the diagnostic methods is needed. This research departs from the common classification of diagnostic products used in market research which have fuzzy boundaries (The Lewin Group Group, 2005). We create and adopt a classification for the type of knowledge base that is needed for the development of the diagnostic product.

[5] The official term used by the FDA is product code, we adopt the term "product class" because it is semantically closer to the use that we make of it in this research.

We make clear division based on the *technique* that the product utilizes to identify and/or measure the biomarker.

Gene patents cover sequences of nucleic acid nature. Nucleic acids are the building blocks of genes and genetic information in general. A gene patent claim propriety rights for use over whole gene sequence or just some sequence fragments. For our analysis we distinguish products that use nucleic acids as biomarkers from those that use proteins and other substances.

The techniques that target nucleic acids were developed and diffused in diagnostic practice after those that target proteins. Table 1 reports the diagnostic techniques developed and adopted during the 20th and 21st century. Table 1 also reports the time of adoption of the technique in the diagnostic practices according to the literature.

Table 1 Type of techniques and period of adoption in diagnostics.

Proteins		**Nucleic acids**	
Serology	1900s	PCR techniques	'80s
Biochemistry	1900s	FISH	'80s
Staining	'20s	Genotyping	2000
Cell culture	'70s	Sequencing	2010s
Immunoassays	'80s	Chromogenic in situ hybridization (CISH)	2010s
Immunohistochemistry (IHC)	'80s		

Now that the scientific background of the categorization has been introduced we are going to address products in two macro classes with a clear link to the literature. This will facilitate reading and comprehension:

- All the techniques that involve nucleic acids will be addressed as DNA technology
- All the techniques that do not involve nucleic acids will be addressed as non-DNA technology

3. Theory

This section develops as follow: first the criteria to evaluate product supply are discussed and contextualized in the diagnostic industry. Then theory on the privatization and exploitation of knowledge is illustrated, it follows a discussion on the use of knowledge in product development its dynamics in the diagnostic industry. Hypothesis are introduced.

3.1 Dependent variable: Product Supply

The phenomenon we are interested to study is quality of product supply especially to the extent to which product improvements take place and monopolistic markets are avoided.

Quality and speed of knowledge production impact technology and growth (Shapiro, 2001). Thus we assume knowledge production also affects the quality of product supply in the IVD industry. In 1776, Adam Smith was the first to highlight this relationship describing 'technology as an intermediate between

science and growth' (Stephan, 1996, pp1226), and subsequent studies proved that scientific advance is fundamental for technological advance and growth (Adams, 1990; ISI, 1993; Mansfield, 1995).

The patent system has been proven to support the production of technological products and it has a positive influence on social welfare (Hellmann, 2007; Kitch, 1977). It creates a market for ideas where knowledge producers and technology developer can match their interest, collaborate and exchange knowledge (Hellmann, 2007). On the other hand patenting cuts out competitors and supports the formation of monopolies (Kitch, 1977; Wilson, 2012). In turn, the lack of competitors decreases incentives for companies to invest in product innovation and improvement (Sevilla et al., 2003). Which has a negative effect on product supply (Sevilla et al., 2003).

This research evaluates the quality of product supply with three criteria: number of incremental innovations, level of monopoly, and strength of barriers to entry.

3.1.1 Number of incremental innovations

The investment and efforts that a company puts in R&D converge into innovations that are embodied in new products (Abernathy & Utterback, 1978). This study considers products in the same niche manifestations of incremental innovations. Such incremental innovations are deemed to bring better services than the previous ones (Abernathy & Utterback, 1978). An example of such incremental innovations in the diagnostic industry are products that provide more accurate and precise results, or to deliver a diagnosis in a sensibly shorter time (The Lewin Group Group, 2005).

Therefore higher number of products indicates higher quality of product supply.

3.1.2 Strength of monopoly

When products are supplied by different companies innovative efforts may be even more exacerbate by the attempt to gain a competitive edge on competitors and outplay them (Teece, 1986; Tidd, Bessant, & Pavitt, 2005). This competitive edge leads to products of higher quality(Tidd et al., 2005). The presence of competitors in a niche also promote the exploration of more than one technological approach and supply product that can probabilistically perform better than product realized exploiting a single technological approach[6] (Arthur, 1989; Cohen & Merril, 2003). In fact companies have the tendency to maintain routines that have been proven successful in the past and oppose to change (Nelson & Winter, 1977), thus rarely a company explores more than a technological approach (Cohen & Merril, 2003)

Patenting is a tool for companies to lock out competitors from a market and in so doing creating a monopoly (Cohen et al., 2000). Such situation is to be avoided since it leads to poor level of product and services, lack of costumer sovereignty and outdated services (Sevilla et al., 2003).

Therefore lower level of monopoly indicates higher quality of product supply.

3.1.3 Strength of the barriers to entry

Firms may attempt to establish a monopoly (Cohen et al., 2000). However, competitors may disregards the difficulties and pursues their goal of entering the niche (Cohen & Merril, 2003). In this process overcoming the barriers to entry is a time consuming activity. As argued above patenting is one of the strategy used to block competitors, whom are left with the choice of inventing around or quit their project (Cohen & Merril, 2003). Therefore the difficulty in inventing around are reflected in the time needed for

[6] This is discussed in depth in the 'Licensing in the diagnostic industry' subsection

a competitor company to introduce its own product in the niche. Once a competitor is in the niche the absolute monopoly is broken. In turn, this starts the virtuous effects of competitions that lead to timely incremental innovations and explorations of technological solutions.

Therefore weaker barriers to entry indicate more potential for higher quality of product supply.

We are now going to introduce the theoretical framework of this research that is grounded on modalities of access and exploitation of knowledge.

3.2 Economics of science

Economics of Science (EoS) has a broad body of literature that describes the several interactions that take place in the production of knowledge and its use for downstream product development (Dasgupta & David, 1994; Stephan, 1996). EoS describes the actors and institutions involved in the production of science-derived products while including their goal and motivations in the picture (Ibid.). In particular it highlights the different reward systems in the academy and in the industry (ibid). While in the academy open sharing of resources and results is rewarded in the industry secrecy and control of resources is encouraged (Ibid.). This is well described by Murray (2002, pp1390) 'Science […] is characterized by publication, supported by a priority-based reward system and exists predominantly (but not exclusively) in research universities. This is in contrast to the world of technology in which ideas are produced for economic ends and encoded in patents and other modes of protection to facilitate appropriability'. Adopting EoS concepts is possible to get a snapshot at the state of the art in diagnostic development not only from a purely technological stand point but also sociological (Fiona Murray, 2002).

3.2 .1 Modalities of knowledge disclosure and their influence on

Dasgupta and David (1994) define two different behaviors of knowledge disclosure: public and private. Actors involved in science tend to apply full disclosure of their knowledge due to the priority reward system based on a winner takes it all scheme and because of the self-reward obtained by solving a puzzle (Stephan, 1996). However it is not unlikely that research is undertaken with the intent of selling the result in secrecy to the industry, or that knowledge is withheld in tacit form for trading it (Dasgupta & David, 1994). In the first instance knowledge disclosure is public while in the second is private. The adoption of private disclosure is due to a failure in the market mechanism which "has a tendency to discourage the production of public goods because of an inability on the part of producers to appropriate fully the value of the fruits of their efforts " (Dasgupta & David, 1994, pp497).

One solution to this issue is granting propriety rights over the discoveries and allowing them to charge fees on the utilization of the knowledge (Dasgupta & David, 1994). In 1980 the Bayh Dole Act allowed and encouraged universities to patent and license their inventions with the aim to promote their utilization and dissemination (Nicol & Nielsen, 2003). Patenting of DNA related technologies followed closely after the Bayh Dole Act came into effect (Cho et al., 2003; Nicol & Nielsen, 2003).

On the one hand, this policy is a solution to the problem of secrecy in public research. It was praised for its effects on patent filing and private investment (Subcommittee on Patents, Copyrights, and Trademarks, 1994). On the other hand patenting can also cause knowledge to be monopolized and underused, both in upstream research and downstream product development (Kitch, 1977; Fiona Murray & Stern, 2007)

The work of Furman and Stern (2006) is a fundamental contribution to the understanding of the microeconomics of knowledge exploitation. They studied the microeconomics of cumulativeness by

investigating what the effect is of depositing research material for public use[7] and its subsequent use (Ibid.). Their study proved that accessing and employing the research material has a crucial role for knowledge production and improvement (Ibid.).

It is conventional thinking that open access and exploitation of these R&D activity ensure their optimal use, yet evidences show that a level of knowledge privatization is necessary to start the entrepreneurial process that transform knowledge and technology into actual products with a societal goal (Cohen & Merril, 2003; Pressman, 2012). In fact the patents motivate the companies to undertake the risks that are involved in R&D, the trade of for the risk of the initial investment is the granting of a monopoly on the use of the technology developed from the research effort for a 20 year period (The Lewin Group Group, 2005). As The Lewin Group (2005) points out "Without the prospect of patent protection, there would be little incentive for diagnostics firms to undertake R&D projects at considerable expense and risk." (pp 62). Studies suggest that the patents seems to positively influence the advancement of biomedical R&D (The Lewin Group Group, 2005). In 2003 a study from the National Research Council showed that patents were increasing in number and complexity but not in a way that would prevent competitors from developing products (Cohen & Merril, 2003). Therefore, so far the hypothesis advanced by Heller and Eisenberg haven't found solid proofs.

3.3 Independent variables: Modalities of knowledge access

In the remainder of the theory section we are going to illustrate different ways of knowledge and material sharing in the "Republic of Science" and the industry. It is hypothesized that different behavior of actors in the realm of science and technology has an influence on the quality of supply diagnostic products.

3.3.1Sharing

Knowledge sharing is a strong feature of science (Dasgupta & David, 1994; Stephan, 1996). However its priority based reward mechanism gives reason for adopting secrecy in certain situations (Ibid.). Walsh & Hong (2003) found that the increase of general secrecy in science is linked to a fiercer competition in research and to industry funding. Collaboration with industry was found to have a minor influence and patenting had none (ibid.). At a finer resolution it has been observed that access to knowledge has not been affected in the past years (Cohen & Merril, 2003), but material has been shared less (Campbell & Clarridge, 2002; Eisenberg, 2001; Walsh et al., 2005). The main reasons for the missed sharing of resources among scientists are the burden of the request and the ability to publish years (Walsh et al., 2005). Commercial implications had a minor influence (Ibid.), but the fact that a patent was pending over the material or not had no influence (Ibid.).

The "Republic of Science" disregards the patenting laws to a large extent and there is a strong common sense for open access and sharing (Caulfield et al., 2006; Murray, 2010; Walsh et al., 2005). Moreover, actors in the industry are reluctant to enforce their IP privilege on the scientific community because the use of the technology may enhance its commercial value and because legal action could backfire on the image of the company (Walsh et al., 2003b). At the same time industry actors claim that legal action would be undertaken when instead it would be a competitor who infringes on the patent (Ibid.).

This contrast highlights the different institutional logic in science and technology (Stephan 2013). Given the cumulative nature of technology, the shortage of sharing among actors in the industry, and the little

[7] In Biology and related Sciences research material can be considered an equivalent of codified knowledge.

impact that commercial implication have on the sharing behavior of academic it can be hypothesized public research efforts are an important contribution to the advancement in the industry.

Even when a resource is offered in exchange, actors in the science realm and in the technology realm have different degrees of secrecy and different interests (Dasgupta & David, 1994). While actors in the industry have an interest in keeping exclusivity in resource use, academics are interested in promoting the use of the resources they produced (Dasgupta & David, 1994), therefore when a resource is patented by a public institute it is more easily accessible facilitating in turn its employment in product development. It follows that *public nature of the IP assignee has a positive influence on the quality of product supply.*

Sharing in the diagnostic industry

An important factor that characterize the competition in the diagnostic industry is the heavy reliance on patents (The Lewin Group Group, 2005). As discussed earlier the foundation of the diagnostic industry make it so that the patenting of a biomarker can assignee strong IP rights and diagnostic companies strive for patenting biomarkers.

It is argued that genetic diseases can be diagnosed from gene sequencing or from the protein that is produced from the gene and other downstream manifestation of altered physiology conditions(Pressman, 2012) For this reason companies do not only aim to patent the biomarker (Cohen & Merril, 2003). Companies aim for patenting the upstream cause in the form of a biomarker and cut out the competitors from conducting research that could threat their market (ibid.). As stated by a respondent in an interview "Your competitors find out that you've filed against anything they might do. They complain, 'How can we do research?' I respond, 'It was not my intent for you to do research.'" (Cohen & Merril, 2003, pp. 310).

In this light it is logical to consider 'restrictions on the use of biomarkers'[8] through patenting and exclusive licensing to be common practice in the diagnostic industry (Cohen & Merril, 2003). These practices privatize the knowledge and potentially decreases the quality of product supply. To test the whether this is true the following hypothesis is formulated

HP1.1: The presence of IP rights covering a particular market niche has a negative influence on the quality of product supply in that market niche.

The chance to assert propriety rights over their discoveries encourages public institutions to push them to companies, thus supporting knowledge production diffusion and exploitation (Dasgupta & David, 1994; Hellmann, 2007) . On the contrary companies use private knowledge to block competitors and to maximize their economic returns, even at the cost of knowledge diffusion and exploitation (Cohen & Merril, 2003). Therefore the IP rights assigned to private companies have a negative influence on the quality of product supply.

HP1.2: The private nature of the assignee of IP covering a particular market niche has a negative influence on the quality of product supply in that market niche.

3.3.2 The cost of licensing

When knowledge is not being shared free of cost it may still be accessible for a fee (Walsh et al., 2005). On this point Nicol and Nielsen (2003, pp12) argue that 'if license fees are too high or if license terms are

[8] Cohen and Merril 2003 call this 'restriction on the use of target' including both the pharmaceutical and diagnostic industry, we address the target ad biomarker due to our focus on the diagnostic industry.

too restrictive this may have a detrimental effect on the capacity of […] research institutions to carry out their research programs and on the capacity of diagnostic facilities to continue to offer diagnostic tests'. However studies on upstream research tool indicate that while some firms and researchers are denied access to certain technology, others have access to it (Caulfield et al., 2006). This indicates that access to the technology is likely to be related to the willingness to accept the terms of use and market prices more than unwillingness to cooperate of the upstream IP holder (Caulfield et al., 2006; Cohen & Merril, 2003; Cohen, 1999). Results from the studies of Furman and Stern (2006) on biological resource centers (BRC) confirm that higher prices relate to lower consumption of research material. BRC are biological resource centers, these are institutions focused on the availability of biological material, often produced from research efforts. BRCs decrease transaction costs for the management of materials and at the same time provide certification for the material quality (ibid).

According to Heller and Eisenberg (1998) transaction costs related to the employment of the IP covered knowledge or product could increase because:

- of the upstream IP rights
- of difficulties in evaluating the value of several techniques involved in the production of a product
- heterogeneity of interest of the involved actors would require costly case-by- case procedures.

Similarly to material sharing an increase in transaction costs of private knowledge causes a decrease in the use of the same and in turn a decrease of the quality of product supply.

The costs of licensing in the diagnostic industry

In the diagnostic industry licensing is practiced, but not without its downsides (Cohen & Merrill, 2003). In a closely related industry, the pharmaceutical industry, potential drug targets are patented to preclude competitors from using them or they are licensed in an exclusive manner, both this practice arm its exploitation (Cohen & Merril, 2003). For example each pharmaceutical firm has a library of molecule that could potentially have therapeutic activity on the target, exclusive use would limit the discovery of a treatment to the molecule in the library of the licensee and according to interviews reported in literature "these odds are not good" (Cohen & Merril, 2003 pp. 311). Moreover when a target is licensed to a company not all the R&D approaches are tested out, as an interviewee reported:

> "Part of the problem that comes in here is that many of these firms are very specialized and many times somebody holds patents but they don't do all the applications feasible. So, what happens is they don't think about doing something and many times the royalty is so high that other companies, small companies that come up with ideas, may not be able to come in and negotiate the license deal. So, it becomes, by default, what happens now. It's not that the patent holder says the idea is great but I'm not going to let anybody do it. But, it never occurs to them. "
> (Cohen & Merril, 2003, pp. 311-312)

This is particularly worrying as the majority of the targets patented from universities are licensed on exclusive basis to small firms (Cohen & Merril, 2003; The Lewin Group Group, 2005). We can imagine that a similar situation takes place in the diagnostic industry, small firms are specialized in a small number of technological approaches and lack the funds to pursue a license from larger firms for the desired technologies (Cohen & Merril, 2003). However the picture that emerges from literature is inconclusive: for example when Chiron, a company holding a patent for hepatitis C protease was challenged from

competitors saying that it was holding deterring innovation with its high licensing prices (Cohen & Merril, 2003). Chiron showed that the patent was licensed to five different diagnostic (ibid.). According to Chiron the accuser where simply not willingly to meet the market price that was agreed with the other five companies (ibid.).

Also the expenses involved in patent negotiation are by no mean trifling. A negotiation implies a $2 million expense over a year (Cohen & Merril, 2003). Whether these expenses limit product development depends on the firm size (Cohen & Merril, 2003). Small firms have limited resources and unlikely to have large funds to invest in pursuing legal negotiation and actions (Cohen & Merril, 2003). On the contrary larger firms are less concerned with the costs (Cohen & Merril, 2003). In fact, despite these sums are not trivial they are dwarfed when compared the funds that these firms invest in R&D (Cohen & Merril, 2003).

More IP rights require more time for negotiations, moreover an increase in number of IP rights lowers the probability that an agreement is found and increase the price for purchasing a useful license (Heller & Eisenbeg, 1998; Shapiro, 2001). Therefore:

HP 2.1: The presence of a higher number of IP rights covering a particular market niche has a negative influence on the quality of product supply in that market niche.

HP 2.2: The presence of a higher number of IP holder of IP rights covering a particular market niche has a negative influence on the quality of product supply in that market niche.

Notice that while HP2.1 focuses on the number of IP rights involved in the market niche HP 2.2 focuses on the number of actors involved in the market niche.

3.3.3 Working out and around IP rights

One of the goal of the patent system is to support the practice of "inventing around" and it does so by limiting access to well-known working solutions (The Lewin Group Group, 2005). On one hand the patent system assigns monopolistic use of an idea to a patent assignee, on the other it incentivize investments in R&D and technological improvements (ibid.).

Evidences show that researchers are likely to invent around IP when clashing with their projects (Cohen & Merril, 2003; Nicol & Nielsen, 2003; OECD, 2003). On this matter, surveys report that interviewees state that in science and technology research there are solutions to work around IP (Nicol & Nielsen, 2003; Walsh et al., 2003). 'Gene patents are said to be special because the book of life is very hard to "invent around" making these patents stronger than in other fields' (Oecd, 2003, pp11). However, studies argue that this is a preconception (Nicol & Nielsen, 2003; Pressman, 2012)[9]. Furthermore, for a project, no more than a dozen of patents requires attention and often none requires licensing (Walsh et al., 2003).It follows that it is rare that IP rights need to be licensed and when it is not possible there are ways to work around the IP (Cohen & Merril, 2003). For example challenging the IP rights in court, move the R&D operations abroad or adopt technological solution that do not infringe on the IP rights (ibid.).

Inventing around previous IP is time consuming and expensive (Nicol & Nielsen, 2003), and in turn this causes a decrease in the quality of product supply. However collaborations are found to favour company entrance and performance in a market niche despite patent protection of the technology underling a

[9] We remand to the original quotes for technicality (Pressman, 2012, pp 4)(Nicol &Nielsen, 2003, pp 213).

market niche (Leten, Belderbos, & Van Looy, 2010). Therefore collaboration has a positive effect on the quality of product supply (Leten et al., 2010).

Working out and around IP rights in the diagnostic industry

Claims and patent validity

When diagnostic companies deal with limited access to biomarkers diagnostic, they adopt several working solutions: pursue a licensee, infringe the IP rights or call the company to court when the patent is deemed invalid especially when the claims are too broad (Cohen & Merril, 2003). As the USPTO website states "Claims point out and distinctly claim the subject matter which the applicant regards as the invention and define the scope of the patent protection."(USPTO, 2014). In other words in the claims the assignee specifies the purpose of the invention and in which context the assignee intends to apply the invention.

The IP system encourages precise claims and patents with poorly specified claims are disregarded by competitors as invalid (Cohen & Merril, 2003). When claims are broad or unclear the patent office may refuse the patents (Cohen & Merril, 2003). Even when such patent is granted competitors are prone to infringe on it and openly challenge its validity (Cohen & Merril, 2003).

Cohen and Merril (2003) found that over a third of the respondent in their survey reported a delay and increase of cost of the research when dealing with patents covering research tools. When a third party asserts patent infringement the infringer can engage into costly patent negotiations or litigations (ibid.).

In alternative to legal actions and negotiations the infringer has also the option to invent around or move operations abroad at cost of a lower quality, delays and the risk of derailing the research (Cohen & Merril, 2003). All options that lead to a lower quality of product supply.

Strategic patenting and licensing

Companies patent their core technologies not to commercialize it but to block competitors from inventing around it (Cohen & Merril, 2003; Leten et al., 2010). This create barriers of entry and force competitors to research and adopt solutions that may be less than optimal (Cohen & Merril, 2003; Leten et al., 2010; OECD, 2003). These patenting activities are found to be effective strategies to deter competitors from obtaining the necessary technological competences to access technological competences and safeguard the financial performance of the company (Cohen & Merril, 2003; Leten et al., 2010). Companies in biotechnology, including IVDs companies, attempt to invent around these patents without infringing on them while trying to gain the competences needed to enter the market niche (Cohen & Merril, 2003; OECD, 2003). Their efforts include agreements that do not limit the potential for future growth and rents obtained from the knowledge and the product developed from them (Cohen & Merril, 2003; OECD, 2003). As the OECD (2003) points out:

> Companies are reluctant to pursue fields of research that will only lead to dependent patents. Certainly, companies rarely set out to improve the inventions of their competitors, but if R&D in a field is already advanced and it appears that an invention is likely to be dependent, companies may try to license, cross-license or even buy the dominant patent. (OECD, 2003, pp.47)

Companies that work around patents have higher chance of successful entry and level of performance if they are involved in collaborations (Leten et al., 2010). Many companies in the IVD industry are engaged in collaborations (OECD, 2003; The Lewin Group Group, 2005). Cohen and Merril (2003) report that for

small companies collaboration is not a choice but a necessity to overcome the barriers to entry due to the high cost of the technology. As stated by one of their respondents referring to a technology in particular:

> "[Technology X is] a high-investment technology. Very small labs can't afford to do it. When the technology is out of reach of small labs, they have to collaborate. But this collaboration generally means giving up IP rights. The technology forces collaboration because barriers to entry are high." (Cohen & Merril, 2003, pp. 302).

Also The Lewin Group (2005) reports that companies in the IVD are active in collaborations. Companies are sometimes involved in a practice known as 'royalty staking', a process where companies collaborate and license several IP rights in the attempt to develop a new product (ibid.). This process could theoretically humper innovation, yet no evidence was found of projects for product development being drop because of 'royalty staking' (ibid.).

Therefore collaborations involving IP rights support the quality of product supply. Hypothesis 3 follows naturally:

HP3: The presence of collaborations involving IP rights in a market niche have a positive influence on the quality of product supply in that market niche.

3.4 Conceptual model

The hypothesis that were previously described are here summarized in Figure 1.

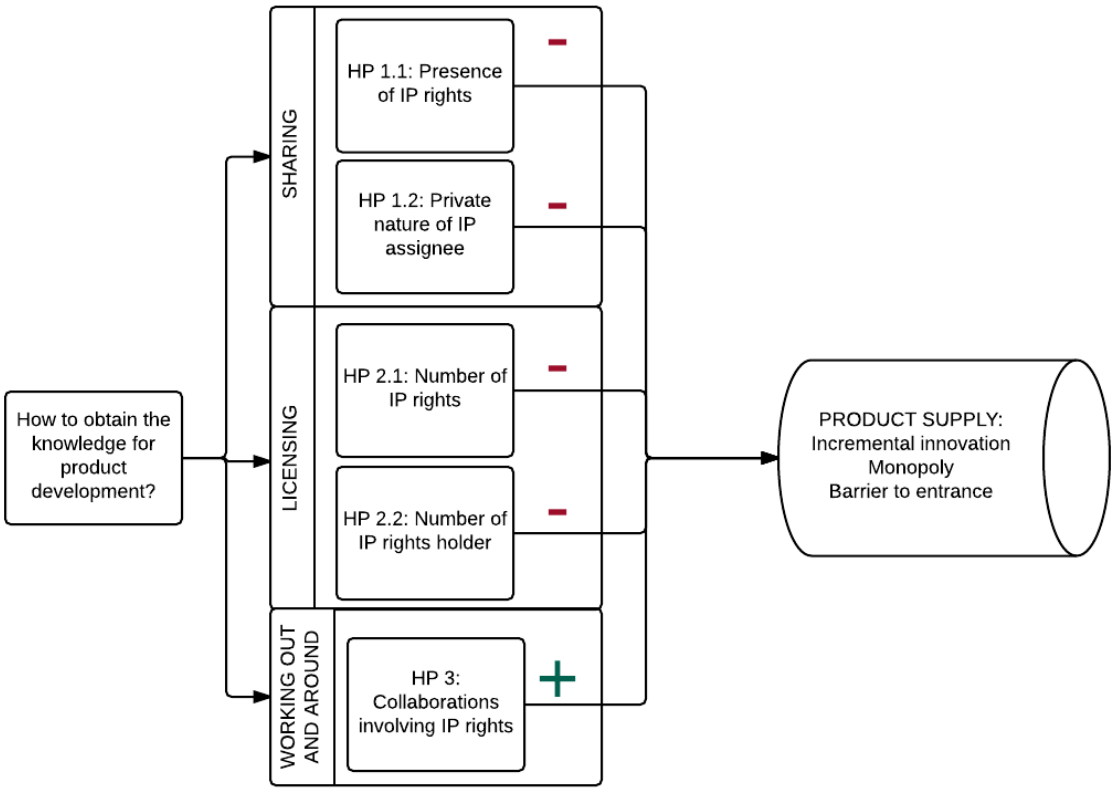


Figure 1 Conceptual model

4. Methodology

This section discuss the research design the data collection and the rationale behind the instruments used for the analysis.

4.1 Research design

This study adopted a quantitative research method and a cross-sectional research design. These were chosen to allow us to investigate a large number of cases and establish the relationship between the variables (Bryman, 2014). These large numbers were necessary to provide a comprehensive picture of the product landscape and break away from previous surveys that only focused on few products (Cho et al., 2003; Merz et al., 2002; Sevilla et al., 2003). A cross-sectional design might limit the validity of the research because long-term time effects are disregarded (Bryman, 2012). We adjust our method to account for this limitation by adopting the Cox Proportional Hazard Model for the analysis of the strength of barriers to entry. This analysis accounts for right censorship to ensure validity of the result despite the use of a cross-sectional design. For the other incremental innovations and strength of monopoly the same analysis is not feasible. For these analysis we minimize the downside of the cross-sectional research design by using a dataset including independent variables from the entire period in which IVD products using DNA technology were approved.

4.2 Data

The data was gathered with the aim to provide a database to investigate the effect of patents on a number of PC. To this aim we sampled PC from the FDA site and then linked them to patents from the USPTO, the final sample is composed of 288 PC. For this link to be made it is crucial that the PC and the Patent indicate with clarity one single disease and one single technology. In the remainder of the section we are going to illustrate how this sample was obtained.

4.2.1 Sampling strategy and data collection

Sampling product classes

We downloaded the list of the whole of the FDA premarket notification and of the premarket notification from the FDA site(FDA, 2016b). This data contained all the PC approved since 1976 to the 6th of May 2016. The total of the PC in the database was 6081. Appendix 1 shows the structure of the FDA database on PC.

We identified IVD classes that use DNA and non DNA biomarkers by searching keywords[10] in the database containing the list of the PC. The databased had fields containing a short description of the classes. We sampled all the PC that contained at least one of the keywords in their description, this procedure returned 520 PCs.

To make sure that all the IVD PC using DNA technology were included in the sample we used the FDA web pages on Nucleic Acid Based Tests and on In Vitro Companion Diagnostic Devices (FDA, 2016e, 2016f). We obtained a total of 96 PC using DNA from these pages, these were also identified from the term search. We performed this step to ensure the validity of our search terms. We couldn't do the same for the techniques using non-DNA biomarkers due to the lack of a page containing such information. However

[10] Complete list of words used for sampling: DNA, RNA, Nucleic Acid, Polymerase, Genotyping, Multiplex, Microfluidic, PCR, ELISA, Immunoassay, Antigen, Antibody, FISH.

the high number of observations suggested that the search terms were sufficiently inclusive of non-DNA PC.

The sample of 520 PCs was cleaned manually to eliminate all the PCs that:

- were not IVDs
- did not specify a Class I, II or III tags
- did not relate clearly to a single disease
- indicate the use of none or more than one technique

After cleaning the sample counted 288 PCs. These are reported in appendix 3.

Sampling patents

We linked the patents to the PC by searching key terms in this the claim section.

The data was retrieved from the USPTO between the 14th and the 22nd of June 2016. To link the data with the PC a search string was composed made of three parts.

- A part to identify patents that "diagnose", "identify", "determine" or "characterize" a substance.
- A part to identify the disease
- And a part that specify which technique is used to carry out the analysis[11]

Combining these three part in a single search the USPTO web service returns the patents that claim a monopoly for the diagnosis of a medical condition using a specific technique. The first part limit the result to diagnostic activities. The second part limits the results to the disease and third part limits the results to the technique. The search strings used to retrieve the patents are reported in appendix 4.

We retrieved patents for the 288 PCs, 102 PCs did not present any patents. The patents in the sample were 2500, excluding duplicates the sample was composed of 1199 patents. Registry of patent ownership transaction were searchable at the USPTO website on the 'Assignment search' web page(USPTO, 2016). Of the total of the patents 982 were licensed. We retrieved a total of 2023 assignment agreements. We cleaned the data on patent licenses so to include only agreements that assigned the right to the use of the IP for product development, this lead to exclusion of security agreements which do not assign right to ownership or use. The final sample was composed of 1602 agreements.

Noise in the data

According to literature patents have a small effect on upstream research and downstream product development.

To avoid high level of noise in the data the researcher sampled patents that were clearly offering an indisputable competitive advantage to the IP holder. This procedure singles out a clear signal even if weak, which according to previous studies is most likely the case (Huang & Murray, 2009; Walsh et al., 2003). Including more patents that do not consider diagnostic as a clear claim would bring a higher level of noise that could cover the signal and provide false negative results.

- [11] This part was retrieved from the description of the PC in the database and grants better specificity than using the classification in techniques.

To permit such level of specificity between the niche and the patents we included in the sample only niches that clearly described the technique they used and the disease they aimed to diagnose. These criteria ensure a strong link between the patents and the PC.

4.2.2 Sample structure and data

Data on PC

We retrieved data on the 288 PCs from the FDA online searchable databases (FDA, 2016c, 2016g) . The 288 PCs reported a total of 621 companies and 3756 products. An overview of the fields available in these databases is reported in the appendix 2.

We retrieved the diagnostic purpose of the PC from the description in the file of the whole of the PCs. For those product that did not provide sufficient insights the researcher used the PC Regulation Number description to retrieve this information (FDA, 2016h). We labelled each PC according to their medical need. A total of 177 purposes were identified.

We used the same procedural steps to label each PC with its specific technique. Serology and immunoassays presented a consistent overlap and where unified under a single label. The techniques where so distributed: FISH (25), Genotyping (16), Immunohistochemistry (11), Nucleic acid amplification (45), Serology (190), Chromogenic in Situ Hybridization (1).The product in each of these overarching principles were as follows: FISH (94), Genotyping (71), Immunohistochemistry (40), Nucleic acid amplification (332) Serology (2620), Chromogenic in Situ Hybridization (3).

Patent data

The purpose of the patent data is to identify in which PCs ownership of IP rights influenced product supply. To fulfill this we cleaned patent data so that merged companies would count as one assignee. Data on mergers was obtained from web searches for each assignee and from industry blogs and reports.

The patents were labeled according to the type of assignee. Patent assignees were considered public when belonged to a university, hospital, governmental agency or governmental institute.

Assignees were considered private when they were a company, or a corporation. If a university, hospital, governmental agency or institute is associated with an acronym that indicates the involvement in business activities (i.e. inc. or corp. or ltd) the assignee was still considered public. Spinoffs of public institutions were considered as private. This classification is deemed to reflect IP related behaviors described in the theory. Patents that were not given an assignee or that had individuals as assignee where labelled as 'individual'. The patents were so distributed: individual (68), private (789), public (342).

PC-Patent link

The aim of linking PC and patents is to provide a clear dataset on which to analyze the influence of private knowledge on the development of a PC. To this aim the dataset must report precisely who is the owner of the patent and eliminate patents that were the result of product development.

We linked PCs to the patents according to the search results. We formatted the name of the product applicant, the patent assignee and license assignee entries so that if the applicant and patent owner were the same we would find a direct match.

4.3 Operationalization

4.3.1 Dependent variable

The effect of patents on the quality of the supply of diagnostic products was measured with three criteria which was operationalized as follow:

- the number of incremental innovation was operationalized by the number of products in a PC
- the level of monopoly was operationalized by the level of market concentration in a PC using the Herfindahl-Hirschman Index –(HHI)
- the strength of the barriers to entry was operationalized by the difference in time between the first product to be supplied in a product class and the first product supplied by a competitor.

All the dependent variable were interval variables.

Monopoly and Herfindahl-Hirschman Index

The level of monopoly was calculated using the an index of market concentration (Sidak & A. Hausman, 2007). Market concertation is a function of the number of companies and their market share and is a more reliable proxy for monopoly than the plane number of companies or product in the market (Sidak & A. Hausman, 2007).

The HHI was obtained by summing the square of the market share of all the competing companies (Sidak & A. Hausman, 2007). The value of this index go from 10 000 to 0. An index close to 0 suggest perfect competition an index close to 10 000 indicates a monopoly. To calculate the market share we used the number of products of a company in PC over the total number of the products in that PC.

Barriers to entry

We related barriers to the time between the date of entry of the first product in the PC and the date of entry of the second company in the PC. Time to entry was measured in days. The entry time is censored to the right on the 6th of May 2016 , as an entry event was not observed for entering companies.

4.3.2 Independent variable

DNA and non-DNA

The techniques adopted by the PC were used to create a dummy binary variable that indicates whether the PC used DNA or non DNA technology. This binary variable had two values DNA and non-DNA. Value 1 indicate that the PC was based on DNA technology. Value 0 indicate that the PC was based on non-DNA technology.

HP1.1: Presence of IP rights

The presence of IP right was operationalized by a dummy variable with value 1 or 0. Value 1 indicated that at least a patent was linked to the PC. Value 0 indicated that no patent was linked to the PC.

HP1.2: The private nature of the IP assignee

The influence of privatized knowledge was operationalized by calculating the percentage over the total of the patents in that PC.

HP 2.1: Presence of a high number of IP rights

The involvement of high number of IP right was operationalized by count of patents in the product class. This was an interval variable.

HP 2.2: Presence of a high number of IP holders

Fragmentation of the IP rights across multiple holders was operationalized by count of companies that hold patents for that PC.

HP3: Presence of collaborations

We operationalized collaboration by count of licensing agreements related to the patents present in a PC. This was an interval variable and it scores +1 for each of the agreement

4.3.3 Control variable

Age

The age of a PC influenced the number of products and the HHI value in that PC. The older a PC, the more time companies had for developing products.

The age of the PC was calculated by the count of days from the authorization of the first product in class to 6th of May 2016.

Product requirements

Product requirements influences quality of IVD supply as a whole. Higher products requirement decrease the probability that new products were approved, they discourage companies from applying for product approval, and they give a stronger monopoly to companies in that were successful in passing the product approval process.

We operationalized product requirements with the classification used by the FDA. This was an ordinal variable, Class 1 was the lowest level, Class 3 was the highest and Class 2 was in the middle.

Therapeutic class

Therapeutic class control for the effect of market demand on the PCs. Larger markets attracted more competitors than smaller ones. The number of players involved in product development activities had a positive influence on all three of the criteria.

Therapeutic classes used by the FDA were too generic for the level of analysis of this research, therefore the researcher assigned each PC one of the following therapeutic classes: Toxicology, Cancer, Infection, Metabolic Disorder, Organ/System failure, Other. This was a categorical variable.

Table 2 reports how the variables were operationalized.

Table 2 Operationalization table.

Concept	**Variables**	**Indicators**	**Scale**	**Baseline**
Quality of product supply	**Dependent**			
	Incremental innovation	Number of products	Interval	-
	Monopoly	Herfindahl-Hirschman Index	Interval	-
	Barriers to entry	Days of Delay	Interval	-
-	**Control**			
	Age	Days since first product	Interval	-
	Therapeutic Class	Researcher's labels	Categorical	-
	Product requirements	FDA Class	Ordinal	value = Class 1
	Independent			
Sharing	Presence of IP rights	Presence of IP rights	Binary	0(absence)
	Private nature of assignee	% of private assignee	Ratio	
Costs of licensing	High number of IP rights	Number of patents	Interval	-
	Fragmentation of IP rights across multiple holders	Number of companies owning IP in the PC	Interval	-
Working out and around IP rights	Collaborations	Number of licensing agreements	Interval	-
-	DNA product	Technology	Nominal	value = non-DNA

4.4 Accounting for the influence of time on the database

From the data we created two databases. A Database 1 to test the effect of the independent variables on the number of incremental innovations and the strength of monopoly. Database 2 was used to test the independent variables on the strength of the barriers to entry. A Database 1 which was free of any effects from patents obtain by product development and a Database 2 which contained data on the PC at the moment the second company introduced its first product. The data contained in each databases are summarize in table 3.

Patents can protect innovation that will later on used in product development. However patents can also be the result of product development. To isolate this research from errors induced by including in the sample patents that resulted from product development we consider patents and licenses before a well-defined event in a point in time. Before this point patents were only obtained as result of product development were unlikely to be found. This point in time is before the approval of the first product in a PC.

Database 1 was used to test the hypothesis on the number of incremental innovations and the strength of monopoly. The presence of patents, the private nature of IP rights, the number of IP and the number of IP holders, were expected to have an influence on the number of incremental innovations and of level of monopoly. However these independent variables were also influenced by product development. For this reason we registered their value before the first product in class was approved. This gave a clear signal of which patents did not suffer from the knowledge privatization resulted from product development.

The number of collaborations was not influenced by product development yet it was expected to influence the observed number of incremental innovations and the level of monopoly, therefore we used their value to the 6th of May 2016, the date on which data on products was retrieved.

Database 2 was used to test the effect on the hypothesis on the strength of the barriers to entry. The strength of the barriers to entry was expected to be influenced by the patents that were introduced before the first product in class, but also by subsequent patents obtained by product development efforts and filled to blocking competitors. Collaborations and licenses were expected to influence the strength of the barriers. For these reasons in database 2 we use values of the independent variables before the entry of the second company in the PC.

Table 3 Database 1 and Database 2 content.

Obs	**Control variable**				**Independent varaible**					**Dependent variable**		
Product code	Age	Product requirements	Therapeutic Class	DNA or NOT	Presence of patents	Private nature of IP	Number of IP rights	Number of IP rights holder	Number of collaborations	Incremental innovations	Monopoly	/
PC1	To date	Constant	Constant	Constant	Before the 1st in class	Before the 1st in class	Before the 1st in class	Before the 1st in class	To date			
PC2												
PC...												
PC288												
Product code	Age	Product Requirements	Therapeutic Class	DNA or NOT	Presence of patents	Private nature of IP	Number of IP rights	Number of IP rights holder	Number of collaborations	/	/	Barrier to entrance
PC1	To date	Constant	Constant	Constant	Before the 2nd in class	Before the 2nd in class	Before the 2nd in class	Before the 2nd in class	Before the 2nd in class			
PC2												
PC...												
PC288												

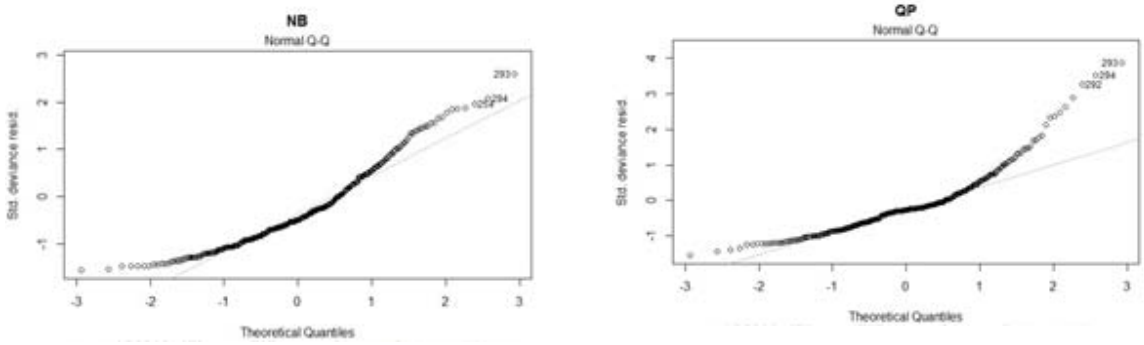
5. Data analysis

A NB (NB) regression model was used to calculate the effects of patents on the number of incremental innovations and the level of monopoly. A cox proportional hazard regression model (COX PHM) was used to calculate the effects of patents on the strength of the barriers to entry.

5.1 Negative Binomial regression model

The nature of the data requires the use of a NB regression analysis. The data was overdispersed. This means that variability in data was greater than was theorized by Poisson distribution where $\mu = \sigma^2$. We calculated the overdisperson value for the dataset with the formula $OD = \frac{1}{n-p}\sum_{i=1}^{n} z_i^2$ We calculated the z-value by comparing observed values with fitted values from the Poisson model. Then we calculated the OD by dividing z^2 by the degrees of freedom. We obtained an OD value of 18.77408 for the number of incremental innovation and of 2299 for the level of monopoly. Any OD value higher than 2 indicates overdispersion.

Thanks to a NB model the interpretation of the results were not influenced by the overdispersion of the data. Quasi Poisson regression models are also commonly used to calculate statistical probabilities in overdispersed datasets. Appendix 8 display statistical distribution of the dependent variables. The choice for the NB regression model was made on the comparison of the QQ plot of the two regression analysis. As shown in figure 3 the NB distribution was closer to the distribution of the data than the Quasi Poisson distribution. A full comparison of the diagnostic graphs of the two regression is available in appendix 5. Other assumptions of the NB such as independence of the data points, distribution of the residuals, and linear relationship between the response and the linear predictor were assessed with diagnostic plots. The plots of models that returned statistically significant results are reported in appendix 6.



Negative binomial QQ plot Quasi Poisson QQ plot

Figure 1 Negative Binomial and Quasi Poisson QQ plot comparison.

A NB regression predicts the probability that a given number of events occurs a number of times in a time/space interval. Predictions were based on the values of the independent variables using the coefficients obtained from the odds ratio. The NB can have two distribution: either the estimation of the dispersion was obtained from the data or a value of dispersion 1 was given and the variance was calculated as $V = \mu + \frac{\mu^2}{\theta}$. In this study the value of the dispersion was obtained from the data.

We checked for the presence of outliers with a graph plotting the Cook distance of the observations. No outlier was found.

We built two a base model (1 and 2), a model to test the variables singularly on the whole of the sample (2 to 8), a model to test the whole effect of the variables (9and 10). To these models we add an interaction to test the effect of the technology employed (10 to 17). Models 1, 8 and 16 account also for the influence of the Therapeutic class, this variable was not included in the other models since was not significant and diminished the degrees of freedom of the model.

We use an Anova test to check for the effective significance of the dummy variables in the model 3 and 4. The test was carried out analyzing the differences between of models 3 and 4 against model 2.

5.2 Cox proportional hazard regression model

To account for the bivariate nature of the dependent variable and the time dimension of the barriers to entry we opt for a cox proportional hazard model (COX PHM). This regression was preferred to NBs because it accounts for right censorship of event. Right censorship was a condition where the value of an observation was only partially known, in our case the entrance of the second company may happens after the moment we gathered the data. A COX PHM accounts for such condition. The cox model specifies the hazard that a second company will enter a PC *i* as the product of a baseline $h_0(t)$ as an exponential function of the model parameters βx and repressors x_i.

A COX PHM had the following formula:

$$h(t,\mathbf{X}) = h_0(t)\exp\left(\sum_{i=1}^{p}\beta_i X_i\right)$$

In semiparametric model using a Weibull distribution the formula takes this form:

$$h(t,\mathbf{X}) = \lambda p t^{p-1} \quad \text{where} \quad \lambda = \exp\left(\sum_{i=1}^{p}\beta_i X_i\right) \quad \text{and} \quad h_0(t) = p t^{p-1}.$$

To properly apply the COX PH two issues must be assessed. The first is non-informative censoring, this was warrant by the research design that ensured that sampling of the observation was not related to the probability of an event occurring.

The second issue was the proportional hazard assumption, meaning that the chance of the event occurring and the chance of the event not occurring must have proportional hazard function overtime. To check if the condition was satisfied we test proportionality of the predictors by looking at the interaction with the logarithm of time to entry. We test the linear correlation between the two with a Pearson product-moment correlation between the scaled Schoenfeld residuals and interaction of logarithm of time to entry and each independent variable. We run the test on the whole model and a significance test to decide if based on the sample there was evidence of correlations. To do so we state a hypothesis 0 for which there was no correlation in the population and a hypothesis 1 stating the opposite. A test on the complete model returning a P value lower than 0.05 indicates that there the proportional hazard assumption was violated. For the models that were found statistically significant these tests are reported in appendix 7.

The COX PHM model returns hazard ratios which are presented with the following formula:

$$HR = \frac{\hat{h}(t, \mathbf{X}^*)}{\hat{h}(t, \mathbf{X})}$$

To interpret the hazard ration the following formula can be used. HR can be interpreted as odds, an increase in HR correspond to an increase in the chance of reaching the event first.

$$HR = \frac{p_i}{1 - p_i} \Rightarrow p_i = \frac{HR}{1 + HR}$$

We built a base model (1), a model to test the variables singularly on the whole of the sample (2 to 7), a model to test the whole effect of the variables (8 and 9). To these models we add an interaction to test the effect of the technology employed (10 to 16). Models 1, 8 and 16 account also for the influence of the Therapeutic class, this variable was not included in the other models since was not significant and diminished the degrees of freedom of the model.

6. Results

6.1 Database 1

6.1.1Descriptive statistics

Table 4 present the descriptive statistics of Database 1, which was created for the analysis of incremental innovations and monopoly.

Table 4 Database 1 Descriptive Statistics

Descriptive statistics

Statistic	N	Mean	St. Dev.	Min	Max
Age	288	8,413.1	4,832.5	50	14,539
NumberOFIPRights	288	1.7	6.1	0	59
PrivateIPRatio	288	0.2	0.3	0.0	1.0
NumberOfIPHolders	288	1.5	5.2	0	50
IncrementalInnovations	288	11.1	20.8	1	179
NumberOfCollaborations	288	11.3	22.2	0	152
HHI	288	5,238.2	3,760.8	253	10,000

6.1.2Correlation table

Table 5 reports the correlation between variables calculated using the Pearson Correlation test. From literature a value of 0.3 or higher indicate a strong correlation. The table shows that the independent variables are strongly correlated.

Table 5 Database 1 Pearson Correlations test

	1	2	3	4	5	6	7
1 Age	1.000						
2 Number Of IP Rights	-0.298	1.000					
3 Private IP ratio	-0.284	0.424	1.000				
4 Number Of IP Holders	-0.299	0.992	0.430	1.000			
5 Incremental Innovations	0.333	-0.079	-0.011	-0.077	1.000		
6 Number Of Collaborations	0.026	0.488	0.330	0.493	0.126	1.000	
7 HHI	-0.451	0.153	0.066	0.159	-0.490	-0.082	1.000

The variance inflated values (VIF) of the models that returned statistically significant results are reported in appendix 6 .

6.1.3 Incremental Innovation results

Tables 6 reports the coefficients and the standard errors models having incremental innovation as dependent variable, table 7 reports the odds ratio. Given the high level of correlation between the IV we are going to discuss only models with a single independent variable.

Table 6 Coefficients and standard errors of the regression models of incremental innovations

	Number of incremental innovations																
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
Age	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0001	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002
	(0.00001)***	(0.00001)***	(0.00002)***	(0.00002)***	(0.00001)***	(0.00001)***	(0.00001)***	(0.00001)***	(0.00002)***	(0.00002)***	(0.00002)***	(0.00002)***	(0.00002)***	(0.00002)***	(0.00002)***	(0.00002)***	(0.00002)***
TherapeuticClassCancer	1.612								1.662								1.684
	(1.105)								(1.082)								(1.079)
TherapeuticClassInfection	1.647								1.453								1.413
	(1.087)								(1.063)								(1.059)
TherapeuticClassMethabolic disorder	1.415								1.250								1.213
	(1.106)								(1.083)								(1.080)
TherapeuticClassOrgan/System failure	1.577								1.462								1.501
	(1.090)								(1.068)								(1.064)
TherapeuticClassOther	1.269								0.884								0.843
	(1.114)								(1.092)								(1.088)
TherapeuticClassToxicology	0.258								0.272								0.275
	(1.113)								(1.088)								(1.083)
ProductRequirements2	0.874	0.724	0.777	0.690	0.721	0.696	0.720	0.717	0.845	0.746	0.741	0.770	0.743	0.770	0.756	0.749	0.818
	(0.157)***	(0.150)***	(0.150)***	(0.150)***	(0.150)***	(0.149)***	(0.150)***	(0.149)***	(0.156)***	(0.149)***	(0.150)***	(0.150)***	(0.150)***	(0.150)***	(0.149)***	(0.152)***	(0.158)***
ProductRequirements3	0.151	0.080	0.106	0.022	0.081	-0.017	0.080	-0.002	-0.158	-0.059	0.043	0.107	0.002	0.107	0.004	-0.055	-0.192
	(0.310)	(0.275)	(0.274)	(0.275)	(0.275)	(0.277)	(0.275)	(0.274)	(0.310)	(0.275)	(0.274)	(0.274)	(0.276)	(0.274)	(0.274)	(0.276)	(0.309)
DNAorNOTDNA			0.462						0.479	0.422	0.469	0.544	0.487	0.534	0.522	0.400	0.442
			(0.171)***						(0.180)***	(0.173)**	(0.197)**	(0.179)***	(0.186)***	(0.180)***	(0.204)**	(0.227)*	(0.230)*
PresenceOfPatentsYES				0.341					0.019	0.076	0.354					-0.065	-0.207
				(0.168)**					(0.288)	(0.288)	(0.213)*					(0.431)	(0.432)
NumberOFIPRights					0.003				-0.067	-0.060		0.014				0.080	0.056
					(0.011)				(0.090)	(0.090)		(0.013)				(0.178)	(0.175)
PrivateIPRatio						0.434			0.287	0.299			0.491			0.435	0.409
						(0.210)**			(0.348)	(0.350)			(0.260)*			(0.517)	(0.515)
NumberOfIPHolders							0.005		0.070	0.054				0.017		-0.100	-0.061
							(0.013)		(0.108)	(0.108)				(0.015)		(0.207)	(0.204)
NumberOfCollaborations								0.008	0.008	0.007					0.008	0.008	0.009
								(0.003)***	(0.003)**	(0.003)**					(0.003)***	(0.003)**	(0.003)**
DNAorNOTDNA:PresenceOfPatentsYES											-0.103					0.400	0.591
											(0.319)					(0.580)	(0.574)
DNAorNOTDNA:NumberOFIPRights												-0.028				-0.234	-0.195
												(0.024)				(0.218)	(0.217)
DNAorNOTDNA:PrivateIPRatio													-0.179			-0.383	-0.293
													(0.416)			(0.713)	(0.702)
DNAorNOTDNA:NumberOfIPHolders														-0.027		0.229	0.161
														(0.030)		(0.261)	(0.261)
DNAorNOTDNA:NumberOfCollaborations															-0.006	0.004	0.004
															(0.010)	(0.014)	(0.014)
Constant	-1.394	0.370	-0.050	0.205	0.357	0.270	0.350	0.314	-1.714	-0.105	-0.179	-0.108	-0.140	-0.113	-0.097	-0.110	-1.690
	(1.114)	(0.192)*	(0.235)	(0.208)	(0.199)*	(0.198)	(0.199)*	(0.193)	(1.101)	(0.247)	(0.246)	(0.242)	(0.239)	(0.243)	(0.236)	(0.247)	(1.097)
N	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288
Log Likelihood	-910.603	-919.419	-916.113	-917.244	-919.391	-917.138	-919.358	-916.395	-902.204	-911.407	-914.214	-915.447	-913.811	-915.561	-913.010	-909.862	-900.291
theta	1.005*** (0.086)	0.950*** (0.080)	0.967*** (0.082)	0.964*** (0.082)	0.950*** (0.080)	0.964*** (0.082)	0.950*** (0.080)	0.969*** (0.082)	1.061*** (0.092)	0.999*** (0.085)	0.980*** (0.083)	0.969*** (0.082)	0.982*** (0.083)	0.969*** (0.082)	0.986*** (0.084)	1.007*** (0.086)	1.072*** (0.093)

Notes:

***Significant at the 1 percent level.
**Significant at the 5 percent level.
*Significant at the 10 percent level.

Table 7 Odds Ratios of the regression models of incremental innovations.

	Number of incremental innovations																
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
Age	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
TherapeuticClassCancer	5.015								5.268								5.389
TherapeuticClassInfection	5.191								4.276								4.108
TherapeuticClassMethabolic disorder	4.119								3.491								3.365
TherapeuticClassOrgan/System failure	4.840								4.315								4.485
TherapeuticClassOther	3.559								2.419								2.324
TherapeuticClassToxicology	1.295								1.312								1.316
ProductRequirements2	2.395	2.062	2.176	1.993	2.057	2.005	2.055	2.048	2.328	2.109	2.098	2.161	2.102	2.159	2.129	2.114	2.265
ProductRequirements3	1.164	1.083	1.112	1.022	1.084	0.983	1.084	0.998	0.854	0.943	1.044	1.113	1.002	1.113	1.004	0.947	0.825
DNAorNOTDNA			1.588						1.614	1.525	1.598	1.722	1.628	1.705	1.686	1.492	1.555
PresenceOfPatentsYES				1.406					1.019	1.079	1.425					0.937	0.813
NumberOFIPRights					1.003				0.935	0.942		1.014				1.083	1.058
PrivateIPRatio						1.543			1.332	1.348			1.633			1.545	1.506
NumberOfIPHolders							1.005		1.072	1.056				1.017		0.905	0.941
NumberOfCollaborations								1.008	1.008	1.007					1.008	1.008	1.009
DNAorNOTDNA:PresenceOfPatentsYES											0.902					1.492	1.805
DNAorNOTDNA:NumberOFIPRights												0.972				0.791	0.823
DNAorNOTDNA:PrivateIPRatio													0.836			0.682	0.746
DNAorNOTDNA:NumberOfIPHolders														0.973		1.257	1.175
DNAorNOTDNA:NumberOfCollaborations															0.994	1.004	1.004
Constant	0.248	1.448	0.951	1.228	1.429	1.310	1.420	1.369	0.180	0.900	0.836	0.898	0.870	0.893	0.908	0.896	0.185
N	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288
Log Likelihood	-910.603	-919.419	-916.113	-917.244	-919.391	-917.138	-919.358	-916.395	-902.204	-911.407	-914.214	-915.447	-913.811	-915.561	-913.010	-909.862	-900.291
theta	1.005*** (0.086)	0.950*** (0.080)	0.967*** (0.082)	0.964*** (0.082)	0.950*** (0.080)	0.964*** (0.082)	0.950*** (0.080)	0.969*** (0.082)	1.061*** (0.092)	0.999*** (0.085)	0.980*** (0.083)	0.969*** (0.082)	0.982*** (0.083)	0.969*** (0.082)	0.986*** (0.084)	1.007*** (0.086)	1.072*** (0.093)
Akaike Inf. Crit.	1,841.205	1,846.838	1,842.227	1,844.488	1,848.782	1,844.276	1,848.716	1,842.791	1,836.407	1,842.814	1,842.427	1,844.894	1,841.622	1,845.122	1,840.020	1,849.723	1,842.582

Notes:

***Significant at the 1 percent level.
**Significant at the 5 percent level.
*Significant at the 10 percent level.

To determine whether the categorical variables have an effect on the variable as a whole it is necessary to compare the model including the categorical variable with a constrained model. Table X reports Anova test we used to test whether the dummy variables have an effect on the number of products as a whole:

```
                                  Model     theta Resid. df    2 x log-lik.   Test    df LR stat.     Pr(Chi)
1            Age + ProductRequirements 0.9495136       284       -1836.838
2 Age + ProductRequirements + DNAorNOT 0.9666250       283       -1830.227 1 vs 2     1  6.61122 0.01013382
```

Figure 2 Anova test for the statistical significance of the type of technology as predictor of incremental innovations.

```
                                  Model     theta Resid. df    2 x log-lik.   Test    df LR stat.     Pr(Chi)
1                    Age + ProductRequirements 0.9495136       284       -1836.838
2 Age + ProductRequirements + PresenceOfPatents 0.9636612       283       -1832.488 1 vs 2     1 4.350354 0.03700124
```

Figure 3 Anova test for the statistical significance of the presence of patents as predictor of incremental innovations.

Hypothesis 1.1 predicts that the presence of IP rights covering a particular market niche has a negative influence on the number of incremental innovations in that market niche. In contrast with this prediction the coefficient for the number of incremental innovations is positive and statistically significant (β=0.341; $p<0.05$; OR= 1.406). The Anova found this dummy variable to be statistically significant ($p<0.05$).

Hypothesis 1.2 predicts that private nature of the assignee of IP covering a particular market niche to have a negative influence on the number of incremental innovations that market niche. Model 6 reject this hypothesis, and suggests that instead the private nature of IP assignee in a market niche has a positive influence on the number of incremental innovations in that market niche. The coefficient for this predictor is positive and significant (β=0.434; $p<0.05$; OR= 1.543).

Hypothesis 2.1 and 2.2 predict that the presence of a higher number of IP rights and IP rights holders in a market niche have a negative influence on the number of incremental innovations in that market niche. The models do not provide any evidence to sustain these claims.

Hypothesis 3 predicts that collaborations involving IP rights in a market niche have a positive influence on number of incremental innovations in that market niche. Model 8 supports this hypothesis, the coefficient of the predictor is positive and significant (β=0.008; $p<0.01$; OR= 1.008).

This researcher hypnotizes that the technology used in a market niche has an influence on the number of incremental innovations in that market niche. Model 3 support this hypothesis, the coefficient for DNA technology is positive and significant (β=0.462; $p<0.01$; OR= 1588). The Anova test also confirmed that the technology has an influence of the number of incremental innovations ($p>0.05$)

The hypothesis are considered as a whole in models 9 and 10. According to these models only the type of technology and the number of collaborations involving IP have an influence on the number of incremental innovations.

The question that drives this research is whether patenting of DNA have different effects than patenting of other type of material, from the analysis it appears that the type of patenting in a market niche does not affect the number of incremental innovations in that market niche.

6.1.4 Level of monopoly results

Tables 8 reports the coefficients and the standard errors of the models having level of monopoly as dependent variable, table 9 reports the odds ratio.

Due to the high level of correlation between the IV wee are going to discuss solely the models with a single independent variable.

Table 8 Coefficients and standard errors of the level of monopoly.

	Level of monopoly strenght																
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
Age	-0.0001	-0.0001	-0.0001	-0.0001	-0.0001	-0.0001	-0.0001	-0.0001	-0.0001	-0.0001	-0.0001	-0.0001	-0.0001	-0.0001	-0.0001	-0.0001	-0.0001
	(0.00001)***	(0.00001)***	(0.00001)***	(0.00001)***	(0.00001)***	(0.00001)***	(0.00001)***	(0.00001)***	(0.00001)***	(0.00001)***	(0.00001)***	(0.00001)***	(0.00001)***	(0.00001)***	(0.00001)***	(0.00001)***	(0.00001)***
TherapeuticClassCancer	0.261								0.377								0.297
	(0.747)								(0.740)								(0.735)
TherapeuticClassInfection	0.428								0.475								0.437
	(0.735)								(0.727)								(0.721)
TherapeuticClassMethabolic disorder	0.035								0.146								0.052
	(0.749)								(0.742)								(0.736)
TherapeuticClassOrgan/System failure	0.384								0.468								0.427
	(0.737)								(0.731)								(0.725)
TherapeuticClassOther	0.840								0.876								0.821
	(0.753)								(0.746)								(0.740)
TherapeuticClassToxicology	0.843								0.849								0.834
	(0.752)								(0.744)								(0.738)
ProductRequirements2	-0.464	-0.460	-0.464	-0.444	-0.462	-0.449	-0.462	-0.467	-0.495	-0.486	-0.459	-0.466	-0.467	-0.467	-0.468	-0.487	-0.515
	(0.107)***	(0.102)***	(0.102)***	(0.102)***	(0.102)***	(0.102)***	(0.102)***	(0.101)***	(0.107)***	(0.102)***	(0.102)***	(0.102)***	(0.102)***	(0.102)***	(0.102)***	(0.103)***	(0.108)***
ProductRequirements3	-0.173	-0.282	-0.278	-0.243	-0.281	-0.249	-0.281	-0.285	-0.193	-0.256	-0.250	-0.279	-0.249	-0.278	-0.277	-0.239	-0.168
	(0.204)	(0.177)	(0.177)	(0.177)	(0.177)	(0.178)	(0.177)	(0.176)	(0.205)	(0.176)	(0.176)	(0.177)	(0.178)	(0.177)	(0.177)	(0.176)	(0.204)
DNAorNOTDNA			-0.080						-0.040	-0.035	0.027	-0.064	-0.022	-0.062	-0.100	0.018	0.073
			(0.114)						(0.120)	(0.115)	(0.132)	(0.120)	(0.125)	(0.120)	(0.136)	(0.150)	(0.153)
PresenceOfPatentsYES				-0.199					-0.224	-0.301	-0.061					-0.168	-0.062
				(0.113)*					(0.192)	(0.192)	(0.145)					(0.288)	(0.284)
NumberOfIPRights					0.002				-0.026	-0.030		0.004				-0.139	-0.135
					(0.008)				(0.059)	(0.058)		(0.009)				(0.119)	(0.117)
PrivateIPRatio						-0.164			0.110	0.154			-0.042			0.178	0.146
						(0.143)			(0.235)	(0.237)			(0.181)			(0.350)	(0.345)
NumberOfIPHolders							0.003		0.051	0.059				0.005		0.182	0.174
							(0.009)		(0.070)	(0.070)				(0.010)		(0.138)	(0.136)
NumberOfCollaborations								-0.004	-0.005	-0.006					-0.004	-0.007	-0.006
								(0.002)*	(0.002)**	(0.002)**					(0.002)*	(0.002)***	(0.002)**
DNAorNOTDNA:PresenceOfPatentsYES											-0.338					-0.341	-0.371
											(0.215)					(0.386)	(0.380)
DNAorNOTDNA:NumberOfIPRights												-0.007				0.117	0.142
												(0.016)				(0.142)	(0.141)
DNAorNOTDNA:PrivateIPRatio													-0.343			-0.172	-0.229
													(0.284)			(0.480)	(0.471)
DNAorNOTDNA:NumberOfIPHolders														-0.009		-0.130	-0.154
														(0.020)		(0.170)	(0.169)
DNAorNOTDNA:NumberOfCollaborations															0.002	0.006	0.001
															(0.007)	(0.010)	(0.010)
Constant	9.104	9.471	9.525	9.564	9.462	9.509	9.460	9.521	9.129	9.584	9.614	9.517	9.570	9.517	9.571	9.582	9.184
	(0.753)***	(0.127)***	(0.154)***	(0.138)***	(0.131)***	(0.131)***	(0.131)***	(0.128)***	(0.751)***	(0.159)***	(0.159)***	(0.157)***	(0.156)***	(0.158)***	(0.154)***	(0.159)***	(0.744)***
N	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288
Log Likelihood	-2,700.342	-2,709.025	-2,708.757	-2,707.551	-2,708.989	-2,708.409	-2,708.969	-2,707.260	-2,696.607	-2,703.453	-2,706.088	-2,708.622	-2,707.415	-2,708.592	-2,706.958	-2,701.152	-2,693.650
theta	1.886*** (0.146)	1.792*** (0.138)	1.795*** (0.138)	1.807*** (0.139)	1.792*** (0.138)	1.798*** (0.138)	1.792*** (0.138)	1.811*** (0.139)	1.929*** (0.149)	1.852*** (0.143)	1.823*** (0.140)	1.796*** (0.138)	1.809*** (0.139)	1.796*** (0.138)	1.814*** (0.140)	1.877*** (0.145)	1.963*** (0.152)

Notes:

***Significant at the 1 percent level.
**Significant at the 5 percent level.
*Significant at the 10 percent level.

Table 9 Odds ratios of the regression models of the level of monopoly.

	Level of monopoly																
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
Age	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
TherapeuticClassCancer	1.299								1.457								1.346
TherapeuticClassInfection	1.533								1.608								1.549
TherapeuticClassMethabolic disorder	1.036								1.157								1.053
TherapeuticClassOrgan/System failure	1.469								1.597								1.533
TherapeuticClassOther	2.316								2.401								2.272
TherapeuticClassToxicology	2.323								2.337								2.303
ProductRequirements2	0.629	0.631	0.629	0.641	0.630	0.638	0.630	0.627	0.609	0.615	0.632	0.627	0.627	0.627	0.626	0.615	0.597
ProductRequirements3	0.841	0.755	0.757	0.784	0.755	0.780	0.755	0.752	0.825	0.774	0.779	0.757	0.779	0.757	0.758	0.787	0.846
DNAorNOTDNA			0.923						0.961	0.966	1.027	0.938	0.978	0.940	0.905	1.019	1.076
PresenceOfPatentsYES				0.819					0.799	0.740	0.941					0.846	0.940
NumberOFIPRights					1.002				0.974	0.970		1.004				0.870	0.873
PrivateIPRratio						0.849			1.117	1.166			0.959			1.194	1.157
NumberOfIPHolders							1.003		1.052	1.061				1.005		1.200	1.191
NumberOfCollaborations								0.996	0.995	0.994					0.996	0.993	0.994
DNAorNOTDNA:PresenceOfPatentsYES											0.713					0.711	0.690
DNAorNOTDNA:NumberOFIPRights												0.993				1.124	1.152
DNAorNOTDNA:PrivateIPRatio													0.710			0.842	0.796
DNAorNOTDNA:NumberOfIPHolders														0.991		0.878	0.857
DNAorNOTDNA:NumberOfCollaborations															1.002	1.006	1.001
Constant	8,994.915	12,973.060	13,698.310	14,245.980	12,860.190	13,481.520	12,831.650	13,647.370	9,214.211	14,537.100	14,979.920	13,594.340	14,331.760	13,584.350	14,343.360	14,498.350	9,736.368
N	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288
Log Likelihood	-2,700.342	-2,709.025	-2,708.757	-2,707.551	-2,708.989	-2,708.409	-2,708.969	-2,707.260	-2,696.607	-2,703.453	-2,706.088	-2,708.622	-2,707.415	-2,708.592	-2,706.958	-2,701.152	-2,693.650
theta	1.886*** (0.146)	1.792*** (0.138)	1.795*** (0.138)	1.807*** (0.139)	1.792*** (0.138)	1.798*** (0.138)	1.792*** (0.138)	1.811*** (0.139)	1.929*** (0.149)	1.852*** (0.143)	1.823*** (0.140)	1.796*** (0.138)	1.809*** (0.139)	1.796*** (0.138)	1.814*** (0.140)	1.877*** (0.145)	1.963*** (0.152)
Akaike Inf. Crit.	5,420.683	5,426.050	5,427.514	5,425.103	5,427.978	5,426.818	5,427.938	5,424.521	5,425.213	5,426.905	5,426.175	5,431.244	5,428.830	5,431.185	5,427.915	5,432.304	5,429.300

Notes:

***Significant at the 1 percent level.
**Significant at the 5 percent level.
*Significant at the 10 percent level.

As argued before we employ Anova to test the hypothesis that the categorical variable have an effect on number of companies as a whole:

```
                                  Model    theta Resid. df    2 x log-lik.   Test    df   LR stat.    Pr(Chi)
1           Age + ProductRequirements 1.791817       284       -5416.050
2 Age + ProductRequirements + DNAorNOT 1.794659       283       -5415.514 1 vs 2     1 0.5357651 0.4641931
```

Figure 4 Anova test for the statistical significance of the type of technology as predictor of the strength of monopoly.

```
                                     Model    theta Resid. df    2 x log-lik.   Test    df LR stat.    Pr(Chi)
1                  Age + ProductRequirements 1.791817       284       -5416.050
2 Age + ProductRequirements + PresenceOfPatents 1.807498       283       -5413.103 1 vs 2     1 2.947435 0.08601395
```

Figure 5 Anova test for the statistical significance of the presence of patents as predictor of the strength of monopoly.

Hypothesis 1.1 predicts that the presence of IP rights covering a particular market niche increase the chance of a strong monopoly in that niche. In contrast with this prediction the coefficient of the predictor is negative and statistically significant (β=-0.199; p<0.10; OR= 0.923). The Anova test confirms that the presence of patents is a statistically significant predictor of the level of monopoly. More precisely the presence of patents (compared to the absence of patents) multiplies the expected HHI number by 0.923, holding other variables constant.

Hypothesis 1.2 predicts that the private nature of the assignee of IP covering a particular market niche increases the chance of a strong monopoly in that market niche. The analysis did not provided any evidence to sustain this claim.

Hypothesis 2.1 and 2.2 predict that the presence of a higher number of IP rights and IP rights holder in a market niche have a positive influence on the strength of the monopoly in that market niche. The analysis did not provide any evidences to sustain these claims.

Hypothesis 3 predicts that collaborations involving IP rights in a market niche have a negative influence on the strength of the monopoly in that market niche. Model 8 support this hypothesis, the coefficient of the predictor is negative and significant (β=-0.004; p<0.10; OR= 0.996).

The question that drives this research is whether gene patenting has different effects than patenting of other types of material, from the analysis it appears that the type of patenting does not affect the number of incremental innovations in that market niche.

6.2 Database 2

6.2.1 Descriptive statistics

Database 2 was built to consider the time dimension in the entry of a PC or more generally of a market niche. The values of the variables were registered at the moment of the entry of the second company in the niche, for those PC that do not yet have a second company in the PC the values were registered as the 6th of May 2016.

These data are summarized in table 10.

Table 10 Database 2 Descriptive Statistics.

Descriptive statistics

Statistic	N	Mean	St. Dev.	Min	Max
NumberOfIPRights	288	3.7	10.3	0	99
PrivateIPRatio	288	0.3	0.4	0.0	1.0
NumberOfIPHolders	288	3.0	8.3	0	84
NumberOfCollaborations	288	5.0	14.0	0	152
Delay	288	2,964.9	3,766.9	0	14,539

6.2.2 Correlation table

Table 11 reports the correlation between variables calculated using Pearson test to. From literature a value of 0.3 or higher indicate a strong correlation. The table shows that there is a strong correlation between all of the independent variables.

Table 11 Database 2 Pearson Correlation

	1	2	3	4	5	6
1) Age	1.0000					
2) Number Of IP	-0.2087	1.0000				
3) Private IP Ratio	-0.2691	0.3826	1.0000			
4) Number Of IP Holders	-0.2168	0.9907	0.3800	1.0000		
5) Number Of Collaborations	-0.2367	0.9682	0.3635	0.9674	1.0000	
6) Delay	0.2108	0.1138	0.1102	0.1042	0.0979	1.0000

The variance inflated values (VIF) of the models that returned statistically significant results are reported in appendix 7 .

6.2.3 Barriers to entry results

Table 12 reports the coefficients, the standard errors of the models of barriers to entry. Table 13 reports the odds ratio. The poportional hazard assumption held for all of the models except 1, 8 and 17. Given the high level of correlation between the IV we are going to discuss solely the models with a single independent variable.

Table 12 Coefficients and standard errors of the regression models of strength of barriers to entry.

	Barriers to entry																
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
TherapeuticClassCancer	-1.778*								-1.519								-1.531
	(1.041)								(1.045)								(1.045)
TherapeuticClassInfection	-1.582								-1.429								-1.458
	(1.017)								(1.020)								(1.021)
TherapeuticClassMethabolic disorder	-1.194								-1.010								-1.035
	(1.037)								(1.039)								(1.042)
TherapeuticClassOrgan/System failure	-1.708*								-1.408								-1.389
	(1.022)								(1.023)								(1.024)
TherapeuticClassOther	-2.746**								-2.378**								-2.355**
	(1.108)								(1.113)								(1.113)
TherapeuticClassToxicology	-1.666								-1.585								-1.606
	(1.054)								(1.055)								(1.055)
ProductRequirements2	0.673***	0.694***	0.693***	0.758***	0.688***	0.724***	0.691***	0.684***	0.685***	0.747***	0.759***	0.678***	0.717***	0.679***	0.689***	0.730***	0.658***
	(0.187)	(0.176)	(0.176)	(0.176)	(0.175)	(0.176)	(0.176)	(0.175)	(0.191)	(0.177)	(0.176)	(0.176)	(0.176)	(0.176)	(0.176)	(0.179)	(0.194)
ProductRequirements3	0.218	0.165	0.190	0.521	0.367	0.493	0.348	0.307	0.531	0.536	0.496	0.348	0.472	0.321	0.315	0.395	0.393
	(0.360)	(0.317)	(0.319)	(0.326)	(0.322)	(0.326)	(0.321)	(0.321)	(0.379)	(0.330)	(0.327)	(0.327)	(0.328)	(0.326)	(0.325)	(0.337)	(0.375)
DNAorNOTDNA			-0.100						0.065	0.072	0.159	0.064	0.125	0.084	-0.002	0.120	0.146
			(0.168)						(0.203)	(0.189)	(0.230)	(0.190)	(0.204)	(0.191)	(0.197)	(0.231)	(0.244)
PresenceOfPatentsYES				-0.767***					-0.407	-0.418	-0.815***					-0.760*	-0.648
				(0.166)					(0.286)	(0.283)	(0.215)					(0.419)	(0.420)
NumberOfIPRights					-0.059***				-0.085	-0.074		-0.050**				-0.025	-0.017
					(0.018)				(0.095)	(0.094)		(0.022)				(0.124)	(0.119)
PrivateIPRatio						-0.942***			-0.225	-0.266			-0.892***			0.128	0.062
						(0.226)			(0.352)	(0.350)			(0.284)			(0.508)	(0.503)
NumberOfIPHolders							-0.072***		0.005	-0.019				-0.059**		0.105	0.096
							(0.022)		(0.108)	(0.108)				(0.026)		(0.149)	(0.142)
NumberOfCollaborations								-0.036***	0.038	0.043					-0.045**	-0.071	-0.074
								(0.012)	(0.033)	(0.033)					(0.021)	(0.061)	(0.062)
DNAorNOTDNA:PresenceOfPatentsYES											0.006					0.424	0.209
											(0.358)					(0.611)	(0.626)
DNAorNOTDNA:NumberOfIPRights												-0.026				-0.082	-0.145
												(0.039)				(0.209)	(0.211)
DNAorNOTDNA:PrivateIPRatio													-0.198			-0.720	-0.562
													(0.471)			(0.721)	(0.730)
DNAorNOTDNA:NumberOfIPHolders														-0.038		-0.216	-0.129
														(0.048)		(0.253)	(0.252)
DNAorNOTDNA:NumberOfCollaborations															0.015	0.172**	0.173**
															(0.026)	(0.073)	(0.074)
N	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288
R^2	0.108	0.062	0.063	0.135	0.128	0.126	0.128	0.115	0.191	0.162	0.137	0.130	0.127	0.130	0.116	0.185	0.211
Max. Possible R^2	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
Log Likelihood	-940.463	-947.638	-947.458	-936.004	-937.114	-937.475	-937.238	-939.369	-926.317	-931.422	-935.592	-936.883	-937.285	-936.906	-939.148	-927.464	-922.755
Wald Test	29.720*** (df = 8)	17.150*** (df = 2)	17.500*** (df = 3)	38.890*** (df = 3)	27.490*** (df = 3)	34.920*** (df = 3)	27.630*** (df = 3)	25.950*** (df = 3)	50.170*** (df = 14)	41.400*** (df = 8)	39.850*** (df = 5)	27.610*** (df = 5)	35.360*** (df = 5)	27.920*** (df = 5)	25.640*** (df = 5)	44.490*** (df = 13)	52.240*** (df = 19)
LR Test	32.834*** (df = 8)	18.483*** (df = 2)	18.844*** (df = 3)	41.752*** (df = 3)	39.532*** (df = 3)	38.811*** (df = 3)	39.283*** (df = 3)	35.022*** (df = 3)	61.125*** (df = 14)	50.916*** (df = 8)	42.575*** (df = 5)	39.995*** (df = 5)	39.191*** (df = 5)	39.947*** (df = 5)	35.463*** (df = 5)	58.833*** (df = 13)	68.251*** (df = 19)
Score (Logrank) Test	32.649*** (df = 8)	17.777*** (df = 2)	18.127*** (df = 3)	40.395*** (df = 3)	29.355*** (df = 3)	36.467*** (df = 3)	29.556*** (df = 3)	27.533*** (df = 3)	56.513*** (df = 14)	45.245*** (df = 8)	41.484*** (df = 5)	30.877*** (df = 5)	36.986*** (df = 5)	31.185*** (df = 5)	27.864*** (df = 5)	50.211*** (df = 13)	61.304*** (df = 19)

Notes:

***Significant at the 1 percent level.
**Significant at the 5 percent level.
*Significant at the 10 percent level.

Table 13 Odds ratios of the regression models of strength of the barriers to entry.

	Barriers to entry																
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
TherapeuticClassCancer	0.169								0.219								0.216
TherapeuticClassInfection	0.206								0.240								0.233
TherapeuticClassMethabolic disorder	0.303								0.364								0.355
TherapeuticClassOrgan/System failure	0.181								0.245								0.249
TherapeuticClassOther	0.064								0.093								0.095
TherapeuticClassToxicology	0.189								0.205								0.201
ProductRequirements2	1.959	2.001	2.000	2.134	1.989	2.064	1.995	1.982	1.984	2.111	2.137	1.970	2.049	1.972	1.993	2.075	1.931
ProductRequirements3	1.243	1.179	1.209	1.684	1.443	1.637	1.416	1.359	1.701	1.710	1.643	1.417	1.604	1.378	1.370	1.485	1.481
DNAorNOTDNA			0.905						1.067	1.074	1.172	1.066	1.133	1.087	0.998	1.127	1.157
PresenceOfPatentsYES				0.464					0.665	0.658	0.443					0.468	0.523
NumberOfIPRights					0.942				0.919	0.929		0.951				0.976	0.984
PrivateIPRatio						0.390			0.799	0.767			0.410			1.136	1.064
NumberOfIPHolders							0.930		1.005	0.982				0.943		1.111	1.101
NumberOfCollaborations								0.965	1.038	1.044					0.956	0.932	0.929
DNAorNOTDNA:PresenceOfPatentsYES											1.006					1.528	1.232
DNAorNOTDNA:NumberOfIPRights												0.974				0.921	0.865
DNAorNOTDNA:PrivateIPRatio													0.820			0.487	0.570
DNAorNOTDNA:NumberOfIPHolders														0.963		0.806	0.879
DNAorNOTDNA:NumberOfCollaborations															1.016	1.188	1.189
N	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288	288
R^2	0.108	0.062	0.063	0.135	0.128	0.126	0.128	0.115	0.191	0.162	0.137	0.130	0.127	0.130	0.116	0.185	0.211
Max. Possible R^2	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
Log Likelihood	-940.463	-947.638	-947.458	-936.004	-937.114	-937.475	-937.238	-939.369	-926.317	-931.422	-935.592	-936.883	-937.285	-936.906	-939.148	-927.464	-922.755
Wald Test	29.720*** (df = 8)	17.150*** (df = 2)	17.500*** (df = 3)	38.890*** (df = 3)	27.490*** (df = 3)	34.920*** (df = 3)	27.630*** (df = 3)	25.950*** (df = 3)	50.170*** (df = 14)	41.400*** (df = 8)	39.850*** (df = 5)	27.610*** (df = 5)	35.360*** (df = 5)	27.920*** (df = 5)	25.640*** (df = 5)	44.490*** (df = 13)	52.240*** (df = 19)
LR Test	32.834*** (df = 8)	18.483*** (df = 2)	18.844*** (df = 3)	41.752*** (df = 3)	39.532*** (df = 3)	38.811*** (df = 3)	39.283*** (df = 3)	35.022*** (df = 3)	61.125*** (df = 14)	50.916*** (df = 8)	42.575*** (df = 5)	39.995*** (df = 5)	39.191*** (df = 5)	39.947*** (df = 5)	35.463*** (df = 5)	58.833*** (df = 13)	68.251*** (df = 19)
Score (Logrank) Test	32.649*** (df = 8)	17.777*** (df = 2)	18.127*** (df = 3)	40.395*** (df = 3)	29.355*** (df = 3)	36.467*** (df = 3)	29.556*** (df = 3)	27.533*** (df = 3)	56.513*** (df = 14)	45.245*** (df = 8)	41.484*** (df = 5)	30.877*** (df = 5)	36.986*** (df = 5)	31.185*** (df = 5)	27.864*** (df = 5)	50.211*** (df = 13)	61.304*** (df = 19)

Notes:

***Significant at the 1 percent level.

**Significant at the 5 percent level.

*Significant at the 10 percent level.

The Hazard Ratio (HR) is exp (β) and is the relative hazard corresponding to a unit change in the associated predictor while keeping the other variables constant. In this instance you can think of a hazard as an entry rate. So, the greater the number, the weaker the barriers to entry.

Hypothesis 1.1 predicts that the presence of IP rights covering a particular market niche increases the strength of the barriers to entry in that niche. Consistently with this prediction the coefficient for the predictor is negative and statistically significant (β=-0.767; $p<0.01$; OR= 0.464).

Hypothesis 1.2 predicts that the private nature of the assignee of IP covering a particular market niche increases strength of the barriers to entry in that market niche. Consistently with the prediction the coefficient for the predictor is negative and statistically significant (β=-0.942 $p<0.01$; OR= 0.390).

Hypothesis 2.1 predicts that the presence of a higher number of IP rights in a market niche increases the strength of the barriers to entry in that niche. Consistently with the prediction, the coefficient for the predictor is negative and statistically significant (β=-0.059 $p<0.01$; OR= 0.942).

Hypothesis 2.2 predicts that the presence of a higher number IP rights holders in a market niche has a positive influence on the strength of the barriers to entry in that market niche. Consistently with the prediction, the coefficient for the predictor is negative and statistically significant (β=-0.072, $p<0.01$; OR= 0.930).

Hypothesis 3 predicts that collaborations involving IP rights in a market niche have a negative influence on the strength of the barriers to entry in that market niche. Consistently with the prediction, the coefficient for the predictor is negative and statistically significant (β=-0.036, $p<0.01$; OR= 0.965).

This research hypnotizes that the technology used in a market niche has an influence on the strength of the barriers to entry in that market niche. From the analysis the type of technology does not appear to influence the strength of the barriers to entry per se.

The question that drives this research is whether patenting of DNA have different effects that other type of patenting. The interaction effect of the type of technology on the presence of patents can only be observed in model 16. In model 16 the interaction factor between the type of technology and the number of collaborations is significant, however the same does not hold for the univariate analysis. Therefore there are no evidences supporting the claim that DNA patenting has different effects than other types of patenting.

6.3 Result summary

Table 15 reports the hypothesis and their effects on the three criteria as they were discussed above.

Table 14 Result summary. The signs indicate the effect on the quality of product supply.

		Incremental Innovations	Strength of monopoly	Strength of barriers to entry
HP:1.1	Presence of IP	+	+	-
HP:1.2	Private nature of IP	+	0	-
HP:2.1	Number of IP	0	0	-
HP:2.2	Number of owner of IP	0	0	-
HP:3	Presence of collaboration	+	+	-
	DNA technology	+	0	0
	DNA:IP effect	0	0	0

7. Discussion

The aim of this research was to study the influence of DNA patenting on the quality of product supply. The research adopted a quantitative approach departing from all previous studies on the topic, which were based on surveys and interviews (Cho et al., 2003; Cohen & Merril, 2003; Merz et al., 2002; Walsh et al., 2003). This study included multiple dimensions that could be influenced by gene patenting: incremental innovations, strength of monopoly and strength of barriers to entry. A sample of IVD products approved by the FDA was analyzed. The results lead to reject the hypothesis that gene patenting has different effects on product development than patenting of other material. Stronger monopolies are the main concern in literature due to the difficulty related to inventing around genes and the stacking of transaction costs that would make the final product inaccessible (Heller & Eisenbeg, 1998; Nicol & Nielsen, 2003). This research did not find any evidences of these effects.

Despite gene patenting was found to have no particular influence on product development, the analysis revealed that patenting has effects on product development. In particular, contrary to hypothesis 1.1 and 1.2, the presence of patents and private nature of patent's assignee have a positive influence on the number of incremental innovations. Moreover the presence of patents and collaborations have contrasting effects when observed at different point in time of the market lifecycle. Within the limitations of the research, mostly due to data sampling, the research has some theoretical and societal implications.

7.1 Theoretical implications

This research adopted three criteria to bring analytical depth and gather nuanced insights on the effect of patenting on product supply. The research showed that patenting does not affect the product development in a significantly different way than other types of patenting. This rejects the hypothesis advanced by Heller and Eisenberg (1998) that gene patenting would hamper the downstream product

development. This is in line with the findings of Walsh et al. (2003) that suggested that gene patents do not grant an effective monopoly over products or processes and that working solutions around the IP remain within the reach of competitors.

The presence of patents in a market niche promotes the number of incremental innovations in that market and decreases the strength of the monopoly. These results are in line with literature as it suggested that the number of IP rights present in a market niche supports product development and competition (Cohen & Merril, 2003; Pressman, 2012; The Lewin Group Group, 2005). At the same time the presence of patents strengthens the barriers to entry. In line with literature this confirms that patents support the production of technological products, promote competition and at the same time raises the barriers to entry for competitors (Hellmann, 2007; Kitch, 1977; Leten et al., 2010). The presence of patents was found to weaken monopolies. This is in contrast with literature supporting the idea that patents facilitate monopoly. Moreover when comparing the realm of science and the realm of technology, the behaviors are diametrically opposed. While in science a researcher tends to avoid are of study where patenting is present (Cohen & Merril, 2003; Huang & Murray, 2009), our research indicate that companies favor areas where patenting is present.

The private nature of the IP assignee has a positive influence on the number of incremental innovations in that specific market niche. IP rights assigned to companies have higher chances to develop more products than those granted to public institutions. This is in line with the EoS theory as private companies are most likely to transform the produced knowledge to obtain rents (Dasgupta & David, 1994). In line with literature, sustaining that knowledge privatization brings to its monopolization and underuse (Cohen & Merril, 2003; Kitch, 1977; Fiona Murray & Stern, 2007), we found the private nature of IP also strengthens the barriers to entry of the market niche. No clear link between the private nature of IP and the strength of monopoly was found, this opens interesting avenues for future research which will be discussed later on.

The number of IP rights and IP holder do not have a clear effect on the number of incremental improvements in the specific market niche. The two variables also have no clear effect on the level of monopoly. This has rejected the hypothesis of Heller and Eisenberg (1998) that an increase in the number of IP rights and IP holder necessary for product development would hamper product development through an increase in transaction costs. However the number of IP rights and IP holder are also found to increase the barriers to entry for the first successful competitor. This opens interesting avenues for future research which will be discussed further on.

Collaborations have a positive influence on incremental innovations and they weaken monopolies. This is in line with literature (Cohen & Merril, 2003; Leten et al., 2010). Walsh et al., (2003) suggested that companies adopt working solutions around the patents including licensing. Contrarily from what is expected in literature (The Lewin Group Group, 2005; Walsh et al., 2003) collaborations strengthen the barriers of entry. This is in sharp contrast with Leten et al. (2010). According to Leten et al. (2010) companies which work around patents have a higher chance of successful entry and higher level of performance if they are involved in collaborations. This sparks interesting discussion for societal implications and future research, these are discussed below.

Overall, our study corroborate Walsh et al. (2003b) and Caulfield et al. (2006) position that Heller and Heisenberg concerns were reasonable, however the foreseen problems did not manifested and

confirmed that patenting promotes innovation and monopolies at the same time (The Lewin Group Group, 2005)

7.1.2 A time perspective on the evolution of monopoly and innovation in market niches.

Based on results from our models we are now going to propose a model of evolution of innovation and monopoly over the market niche life cycle. Results on the effect of the independent variables on the strength of monopoly and barriers to entry appear contradictory. Observation of the variables used in the models were made at different points in time during the lifecycle of the market niche. This evidence suggests that the effect of patenting on monopoly changes as the market matures.

From the NB models time has a positive influence on the number of incremental innovations and a negative influence on monopoly. From the analysis of the strength of barriers we can say that in market niches that present only one company patenting[12] strengthen the barriers to entrance and therefore strengthen monopolies, we consider the analysis of barriers to entry to represent the situation during the early stages of the market niche. These premises are plotted below.

From the plot in Figure 6 becomes clear that as time passes monopoly strength decreases and innovation increases.

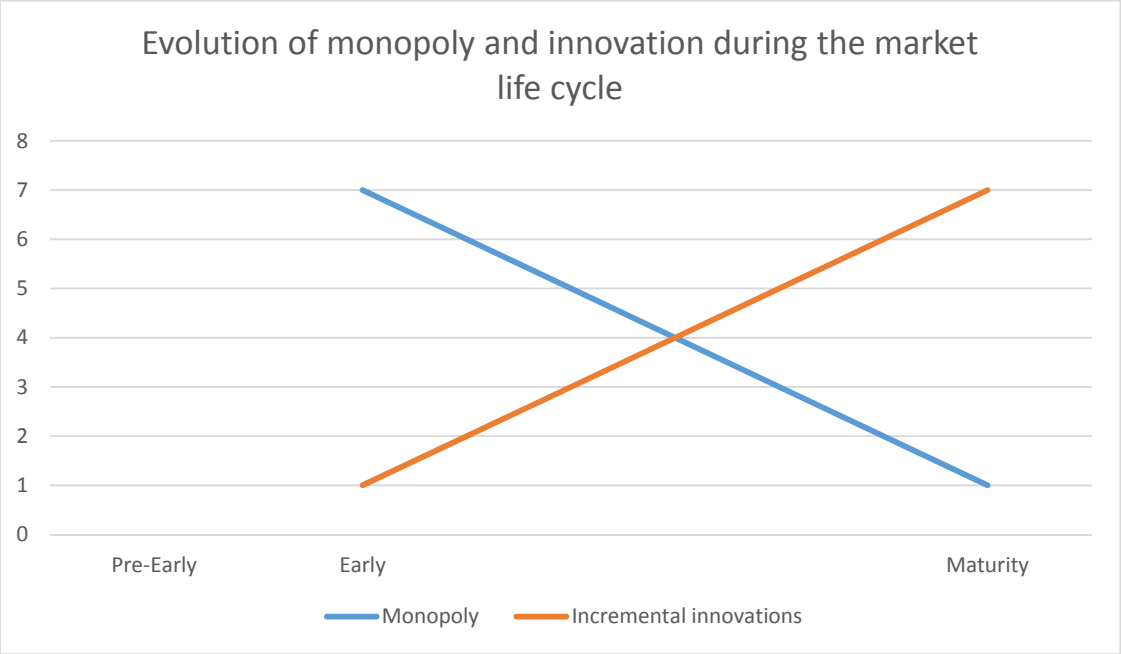


Figure 6 Proposed model of the evolution of the effect of patenting during the market life cycle. Axis X represent time. Axis Y the strength of monopoly and level of incremental innovation on a scale of 0 to 8, 0 indicates a very weak value and 8 a very strong value.

It can be argued that the patents that used for models on incremental innovation and strength of monopoly are different than those used for the barriers to entry. Yet, Database 1 is predictive of the effect observed at the time of maturity and Database 2 is predictive of the strength of monopoly

[12] In the analysis of barriers to entry all the IV are obtained from patent data and have negative coefficients therefore we refer to patenting without going into details.

regardless of time but precisely at the moment of entrance of the second company in the market niche. This event occurs at the early stage of the market niche life cycle(Cefis, 2005).

The models on incremental innovation and strength of monopoly also indicated that patenting activities that take place before the formation of a market niche (Pre-Early stage) are predictive of the future level of monopoly and incremental innovation in the future.

7.2 Societal Implications

Societal implication can be drawn from this study for policymaking of product development in the biomedicine and pharmaceutical sectors.

This study showed that the knowledge privatization in a niche before the formation of a market has a positive effect on the number of incremental innovation in the market niche, especially when private companies are involved in the knowledge privatization. Also, it showed that between the entry in the market of the first and the second company the effects of patenting and collaborations turn from weakening monopolies to supporting them. Policymakers that pursue the goal of facilitating competition and support innovation can direct their effort to those areas of technology that are in early and promising market niches. The purpose of this policy action would be to maintain the mechanism that underlie knowledge production in the pre-early stage and avoid those that arise during the early stage. Further research is needed to uncover these mechanisms, however it is already clear that the involvement of companies in the pre-early stage has a positive influence on incremental innovation. A mechanism that needs to be validated may involve IP fragmentation across patents and actors, this could be a plausible explanation as the commercialization of a first product attracts actors interested in rents and drives knowledge production (Cohen & Merril, 2003; The Lewin Group Group, 2005). The commercialization of the first product coincides with the passage of the niche from pre-early to early. Another mechanism may involve a lack of bargaining power of the patent licensee over knowledge licensing, especially during the early stage of the niche. This is discussed in depth in the section on future research. What policymakers could do if the mechanisms are confirmed by future studies, is to assist licensees in identify and negotiate relevant IP licenses and balance out the supplier power of the IP owner.

The study has also interesting implications for managers in the biomedical and pharmaceutical sectors. The results indicated that patenting is an effective tool for the protection of a market niche. Moreover the results showed that joining in patent licensing is at times a useful practice to disrupt niche monopolies. This was not a measure of direct involvement of product developers in patenting, but a measure of the number of the whole of the licensing agreements involving the patents that cover a market niche. Using this insight managers can interpret the market landscape and identify niches with higher chances of successful product development according to the intensity of patent licensing in the market niche. This strategy must also take into account in what stage of the life cycle is the market niche in as collaboration of in niche at early stages do not favor the entrance of competitors.

7.3 Quality and limitations

The quality of this research was ensured by a solid research design, however it incurred in some limitations. The quality of the research can be better grasped when discussing validity and reliability applied to internal and external dimension.

Internal reliability refers to the stability of the dataset over time (Bryman, 2014). Time, and therefore age of the PC, significantly influence the variables considered in the study. However, we included the age as

control variable in the NB models, thus neutralizing the effects of time on the rest of the variables. The COX PHM observations were not influenced by instability dataset overtime. Therefore the internal reliability of this research is considered to be high.

External reliability refers to the ability to reproduce the results starting from the same sources (Bryman, 2014). We reported the key terms used to sample the data from the FDA website and described in detail the actions that were taken for data gathering. Trivial differences in labeling the diseases could have led to a slightly different pool of patents, but these differences would be so negligible that the dataset would be influenced only superficially. The steps taken to carry out the analysis are reported closely and thus they ensure reproducibility of the results. To further improve external reliability the appendix reports the exact list of PC used in the research and the search strings used to link the patents to the PC. Therefore external reliability of this research is considered to be high.

Internal validity indicate to what extent causal conclusions can be drawn in a satisfactory way (Campbell, 1986). The inclusion of data over 40 year of history of product development and the adoption of regression models accounting for right censorship and likelihood of an event occurring indicate that causal conclusion can be drawn in a satisfactory way. Therefore internal validity of this research is considered to be high.

External validity refers to the extent that the finding of the research are applicable to other fields (Bryman, 2014). Since the FDA is the only institution in charge of granting products to be commercialized in all of the biomedical and pharmaceutical sectors and these sectors adopt similar IP strategy the findings can be extended to these sectors.

This research has some limitations. Firstly, the research did not include the effect of market pull in the analysis. Therapeutic classes were assigned to the market niche, however these classes are a reflection of the classification on the medical condition the IVD address and not of the market. This could affects to some extent external validity of the results.

Secondly, the research did not investigate the presence of multicollinearity in the data. The fact that variables were significant in the univariate analysis, but not in the multivariate analysis suggests that multicollinearity is present in the data. To avoid biased conclusions, we based our interpretations on the univariate models. In these models the independent variables where considered singularly and effects of multicollinearity where excluded.

Finally, a considerable part of the initial sample of PC was eliminated. This omission could have had influences on the findings, especially because of the exclusion of products that address multiple diseases. These products are more likely to be subject to the effect of combination of multiple IPs. Moreover, the sampling of the patents excluded the effects of patents that protect different IP that combined together protect the process of product development. Effects of patenting on these products are expected to be a combination of the various IP needed for product development. Since gene patenting was found to have no effect this these limitations in sampling are not likely to have influenced the main conclusion on influence of gene patenting. The same limitation may have dilute the other effects but not influenced the final conclusions.

7.4 Future research

This study is the first quantitative attempt to define whether or not gene patenting has an effect on downstream product development. It has focused its attention on the heterogeneity of the market niche influences product development. Future research can dedicate more attention to the effect of patenting of the upstream knowledge needed in product development (i.e. how does difference in the patenting of the techniques used in IVD influences product development).

This research found that the private nature of patent assignee has a positive effect on the number of incremental innovations. Pressman (2012) found that exclusive licensing leads to faster product development and approval than non-exclusive licensing. Assuming that private companies rarely license their IP rights these IP rights can be considered closer to the type of ownership that is obtained from exclusive licensing. Future research could investigate if the private nature of the assignee has also an effect on the speed of product development.

Moreover this research pointed out that the presence of patents was found to strengthen the barriers to entrance in the early stages. While at pre-early stages it is a predictor of the level of monopoly at the mature stage. The same holds true for licensing which in the early stages strengthens the barriers to enter and as the niche matures it weakens monopolies. This can be explained by the fact that access to the technology is likely to be related to the willingness to accept the terms of use and market prices of the competitors attempting to entry (Caulfield et al., 2006; Cohen & Merril, 2003; Cohen, 1999). This result is likely to reflect the difference of the licensing conditions in the early and late stages of the market niche.

In the early stages holders of the IP have high bargaining power and can struck agreements that do not arm the monopolistic positions of the IP holders in a considerable manner, moreover the technological potential is not fully understood and crafted (Arthur, 1989; Dosi, 1982). The licensee is in disadvantage at this point of time: with only a restricted number of knowledge provider the licensee suffer of the supplier bargaining power and utilizes resources to pursue a license and develop the immature technology further. This requires the licensee to invest considerable resources in product development. In a mature market niche the knowledge is more likely to be spread among a larger number of companies and the technology is better understood, a number of working solutions were developed and available. In this situation product development is less expensive and resources can be allocated to attempt to enter the market niche. This could explain the contrasting effect of number of IP rights, number of IP holders and especially the number of collaborations, on strengthen of monopoly and strengthen of barriers to entry. Future studies are needed to unravel if whether this is the underling mechanism that drive this phenomena.

8. Conclusion

Drawing from theories of the Tragedy of Anticommons (Heller & Eisenbeg, 1998) and Economics of Science (Dasgupta & David, 1994; Stephan, 1996), we proposed that the type of patented material and a number of other characteristics of patents influence market niches. We measured these influences under three perspectives: incremental innovations, strength of monopoly and strength of the barriers to entry. To study this issue we formulated the following research question

How does gene patenting influences the quality of diagnostic products supply?

The results indicate that gene patenting does not influences the quality of diagnostic products in any particular way. However, they do have an influence on product development as any other patent.

Moreover, the results showed that the effects of patenting in product development have opposite effects than what is seen in research, while scientists are attracted to research in field where there are no patents, companies are drawn to develop products in fields where patents are present.

The results also showed that patents have different influence over the lifecycle of a market nice, they seem to promote a low rate of innovation and high monopoly in the early stages of a market niche and support innovation at the expenses of monopoly. More studies are needed to uncover the mechanisms that drive these changes overtime.

Overall the results confirmed that the patent system promotes both monopolistic control of knowledge and innovative activities. Whether the level of these two activities vary overtime is yet to be answered.

9.Bibliography

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10. Appendix

Appendix 1: Product Code description fields database

1. REVIEW PANEL
2. MEDICAL SPECIALTY
3. PRODUCT CODE
4. DEVICE NAME
5. DEVICE CLASS
6. UNCLASSIFIED REASON
7. GMPEXEMPT FLAG
8. THIRDPARTY FLAG
9. REVIEW CODE
10. REGULATION NUMBER
11. SUBMISSION TYPE ID
12. DEFINITION
13. PHYSICAL STATE
14. TECHNICAL METHOD
15. TARGET AREA
16. Implant Flag
17. Life sustain support flag

Appendix 2.1: Searchable database fields of PMA applications

1. PMANUMBER
2. SUPPLEMENTNUMBER
3. APPLICANT
4. STREET_1
5. STREET_2
6. CITY
7. STATE
8. ZIP
9. ZIP_EXT
10. GENERICNAME
11. TRADENAME

12. PRODUCTCODE
13. ADVISORYCOMMITTEE
14. SUPPLEMENTTYPE
15. SUPPLEMENTREASON
16. REVIEWGRANTEDYN
17. DATERECEIVED
18. DECISIONDATE
19. DOCKETNUMBER
20. FEDREGNOTICEDATE
21. DECISIONCODE
22. AOSTATEMENT

Appendix 2.2: Searchable database fields of k(510) applications

1. KNUMBER
2. APPLICANT
3. CONTACT
4. STREET1
5. STREET2
6. CITY
7. STATE
8. COUNTRY_CODE
9. ZIP
10. POSTAL_CODE
11. DATERECEIVED
12. DECISIONDATE
13. DECISION
14. REVIEWADVISECOMM
15. PRODUCTCODE
16. STATEORSUMM
17. CLASSADVISECOMM
18. SSPINDICATOR
19. TYPE

20. THIRDPARTY
21. EXPEDITEDREVIEW
22. DEVICENAME

Appendix 3 list of the sampled 288 PC

#	Product Code	Class name
1	CZS	Retinol-Binding Protein, Antigen, Antiserum, Control
2	CZW	Complement C3, Antigen, Antiserum, Control
3	DAB	Haptoglobin, Fitc, Antigen, Antiserum, Control
4	DAD	Haptoglobin, Antigen, Antiserum, Control
5	DAH	Gamma Globulin, Antigen, Antiserum, Control
6	DAN	Fibrinopeptide A, Antigen, Antiserum, Control
7	DAP	Fibrinogen And Fibrin Split Products, Antigen, Antiserum, Control
8	DAT	Fibrinogen And Split Products, Peroxidase, Antigen, Antiserum, Control
9	DAZ	Fibrinogen And Split Products, Antigen, Antiserum, Control
10	DBE	Antismooth Muscle Antibody, Indirect Immunofluorescent, Antigen, Control
11	DBF	Ferritin, Antigen, Antiserum, Control
12	DBL	Multiple Autoantibodies, Indirect Immunofluorescent, Antigen, Control
13	DBM	Antimitochondrial Antibody, Indirect Immunofluorescent, Antigen, Control
14	DBT	Factor Xiii A, S, Antigen, Antiserum, Control
15	DCE	Fab, Antigen, Antiserum, Control
16	DCF	Albumin, Antigen, Antiserum, Control
17	DCK	C-Reactive Protein, Antigen, Antiserum, And Control
18	DDB	Ceruloplasmin, Antigen, Antiserum, Control
19	DDC	Thyroglobulin, Antigen, Antiserum, Control
20	DDE	Carbonic Anhydrase C, Antigen, Antiserum, Control
21	DDF	Prothrombin, Antigen, Antiserum, Control
22	DDO	Myoglobin, Rhodamine, Antigen, Antiserum, Control
23	DDQ	Antigen, Antiserum, Control, Antithrombin Iii

24	DDR	Myoglobin, Antigen, Antiserum, Control
25	DDS	Prealbumin, Fitc, Antigen, Antiserum, Control
26	DDT	Alpha-2-Macroglobulin, Rhodamine, Antigen, Antiserum, Control
27	DDX	Plasminogen, Antigen, Antiserum, Control
28	DDY	Alpha-2-Macroglobulin, Fitc, Antigen, Antiserum, Control
29	DDZ	Albumin, Fitc, Antigen, Antiserum, Control
30	DEA	Myoglobin, Fitc, Antigen, Antiserum, Control
31	DEB	Alpha-2-Macroglobulin, Antigen, Antiserum, Control
32	DEF	Alpha-2-Hs-Glycoprotein, Antigen, Antiserum, Control
33	DEG	Lactoferrin, Antigen, Antiserum, Control
34	DEI	Alpha-1-Antitrypsin, Fitc, Antigen, Antiserum, Control
35	DEL	Lipoprotein X, Antigen, Antiserum, Control
36	DEM	Alpha-1-Antitrypsin, Antigen, Antiserum, Control
37	DER	Alpha-1-Lipoprotein, Antigen, Antiserum, Control
38	DFB	Alpha-1-Antitrypsin, Rhodamine, Antigen, Antiserum, Control
39	DFC	Lipoprotein, Low-Density, Antigen, Antiserum, Control
40	DFF	Alpha-1-Antichymotrypsin, Antigen, Antiserum, Control
41	DFI	Total Spinal-Fluid, Antigen, Antiserum, Control
42	DFJ	Albumin, Rhodamine, Antigen, Antiserum, Control
43	DGB	Seminal Fluid, Antigen, Antiserum, Control
44	DGI	Breast Milk, Rhodamine, Antigen, Antiserum, Control
45	DGJ	Colostrum, Antigen, Antiserum, Control
46	DGX	Ng1m(A), Antigen, Antiserum, Control
47	DHF	D/Km-1, Antigen, Antiserum, Control
48	DHI	Ng3m(Bo), Antigen, Antiserum, Control
49	DHN	Antinuclear Antibody, Indirect Immunofluorescent, Antigen, Control
50	DHX	System, Test, Carcinoembryonic Antigen
51	DHY	Ng4m(A), Antigen, Antiserum, Control
52	DJB	Radioimmunoassay, Gentamicin (125-I), Second Antibody Sep.
53	DND	Radioimmunoassay, Digitoxin (125-I), Rabbit Antibody, Solid Phase Sep.

54	DNJ	Radioimmunoassay, Digoxin (125-I), Goat Antibody, 2nd Antibody Sep.
55	DNL	Radioimmunoassay, Digoxin (125-I), Rabbit Antibody, Second Antibody Sep.
56	DOA	Radioimmunoassay, Digoxin (125-I), Goat Antibody, Anion Exchange, Resin Sep.
57	DOE	Radioimmunoassay, Morphine (125-I), Goat Antibody Ammonium Sulfate Sep.
58	DOG	Radioimmunoassay, Digoxin (125-I), Rabbit Antibody, Polyethylene Glycol
59	DON	Radioimmunoassay, Digoxin (125-I), Rabbit Antibody, Solid Phase Sep.
60	DOR	Radioimmunoassay, Digoxin (3-H), Bovine Antibody, Charcoal Sep.
61	DOY	Radioimmunoassay, Digoxin (3-H), Goat Antibody, 2nd Antibody Sep.
62	DPB	Radioimmunoassay, Digoxin (125-I), Rabbit Antibody, Charcoal Sep.
63	DPD	Radioimmunoassay, Digoxin (3-H), Rabbit Antibody, Charcoal Sep.
64	DPG	Radioimmunoassay, Digitoxin (125-I), Rabbit Antibody, Coated Tube Sep.
65	DPJ	Radioimmunoassay, Amphetamine (125-I), Goat Antibody, Ammonium Sulfate Sep.
66	DPO	Radioimmunoassay, Digoxin (125-I), Rabbit Antibody, Coated Tube Sep.
67	GLZ	Antigens, If, Toxoplasma Gondii
68	GMG	Antigen, Latex Agglutination, Coccidioides Immitis
69	GMI	Antigen, Cf And/Or Id, Coccidioides Immitis
70	GMJ	Antigens, Histoplasma Capsulatum, All
71	GMM	Antigens, Iha, Toxoplasma Gondii
72	GMN	Antigens, Cf, Toxoplasma Gondii
73	GMO	Antigen, Latex Agglutination, Entamoeba Histolytica & Rel. Spp.
74	GMQ	Antigens, Nontreponemal, All
75	GMT	Antigens, Ha, Treponema Pallidum
76	GMZ	Antigens, All Types, Escherichia Coli
77	GNC	Antigens, Febrile, Slide And Tube, All Groups, Salmonella Spp.
78	GNE	Antigen, Latex Agglutination, T. Cruzi
79	GNG	Antigens, Cf (Including Cf Control), Coxsackievirus A 1-24, B 1-6
80	GNH	Antigen, Fluorescent Antibody Test, Schistosoma Mansoni
81	GNJ	Antigens, Ha, Echovirus 1-34
82	GNL	Antigens, Cf (Including Cf Control), Echovirus 1-34
83	GNT	Antigens, Ha (Including Ha Control), Influenza Virus A, B, C

84	GNX	Antigens, Cf (Including Cf Control), Influenza Virus A, B, C
85	GOB	Antigens, Ha (Including Ha Control), Adenovirus 1-33
86	GOD	Antigens, Cf (Including Cf Control), Adenovirus 1-33
87	GOL	Antigen, Ha (Including Ha Control), Rubella
88	GON	Antigen, Cf (Including Cf Control), Rubella
89	GOX	Antigen, B. Pertussis
90	GPF	Antigen, Agglutinating, Echinococcus Spp.
91	GPG	Antigen, Latex Agglutination, Trichinella Spiralis
92	GPO	Antigen, Cf, Typhus Fever Group
93	GPS	Antigen, Cf, Q Fever
94	GPW	Antigen, Cf, Psittacosis (Chlamydia Group)
95	GQG	Antigen, Cf (Including Cf Controls), Respiratory Syncytial Virus
96	GQH	Antigen, Cf (Including Cf Control), Cytomegalovirus
97	GQN	Antigen, Cf (Including Cf Control), Herpesvirus Hominis 1,2
98	GQR	Antigens, Ha (Including Ha Control), Parainfluenza Virus 1-4
99	GQS	Antigens, Cf (Including Cf Control), Parainfluenza Virus 1-4
100	GQW	Antigen, Cf, (Including Cf Control), Varicella-Zoster
101	GRC	Antigen, Cf (Including Cf Control), Mumps Virus
102	GRJ	Antigen, Cf, (Including Cf Control), Rubeola
103	GRL	Antigens, All Groups, Salmonella Spp.
104	GRY	Antigens, All, Leptospira Spp.
105	GSB	Antigens, Cf, All, Mycoplasma Spp.
106	GSI	Antigens, Slide And Tube, All Types, Listeria Monocytogenes
107	GSL	Antigens, Slide And Tube, Francisella Tularensis
108	GSN	Antiserum, Positive And Negative Febrile Antigen Control Serum
109	GSO	Antigens (Febrile), Agglutination, Brucella Spp.
110	GTY	Antigens, All Groups, Streptococcus Spp.
111	JNL	Immunochemical, Thyroglobulin Autoantibody
112	JSS	Kit, Identification, Enterobacteriaceae
113	JSZ	Kit, Identification, Pseudomonas

114	JWK	Antigen, Positive Control, Cryptococcus Neoformans
115	JWL	Antigen, Treponema Pallidum For Fta-Abs Test
116	JWT	Antigen, Cf, Aspergillus Spp.
117	JWW	Antigen, Cf, B. Dermatitidis
118	JZH	Factor B, Antigen, Antiserum, Control
119	JZJ	Prealbumin, Antigen, Antiserum, Control
120	JZO	System, Test, Thyroid Autoantibody
121	KHW	Antigen, Id, Ha, Cep, Entamoeba Histolytica & Rel. Spp.
122	KSZ	System, Test, Automated Blood Grouping And Antibody
123	KTL	Anti-Dna Indirect Immunofluorescent Solid Phase
124	KTS	Second Antibody (Species Specific Anti-Animal Gamma Globulin)
125	LGB	Gonococcal Antibody Tests
126	LHK	Antigen, Id, Candida Albicans
127	LHL	Reagents, Antibody, Legionella, Direct & Indirect Fluorescent
128	LHT	Staphylococcus Aureus Somatic Antigens
129	LIA	Antigens, All Groups, Shigella Spp.
130	LIG	Radioassay, Intrinsic Factor Blocking Antibody
131	LIN	Antisera, Conjugated Fluorescent, Cytomegalovirus
132	LIR	Antigen, Enzyme Linked Immunoabsorbent Assay, Neisseria Gonorrhoeae
133	LJB	Enzyme Linked Immunoabsorbent Assay, Rubeola Igg
134	LJM	Antinuclear Antibody (Enzyme-Labeled), Antigen, Controls
135	LJN	Antibody Igm, If, Epstein-Barr Virus
136	LJO	Antigen, Iha, Cytomegalovirus
137	LKJ	Antinuclear Antibody, Antigen, Control
138	LKO	Anti-Rnp Antibody, Antigen And Control
139	LKP	Anti-Sm Antibody, Antigen And Control
140	LKQ	Antibody Igm,If, Cytomegalovirus Virus
141	LKT	Respiratory Syncytial Virus, Antigen, Antibody, Ifa
142	LLH	Reagents, Clostridium Difficile Toxin
143	LLL	Extractable Antinuclear Antibody, Antigen And Control

144	LLM	Test, Antigen, Nuclear, Epstein-Barr Virus
145	LOL	Hepatitis A Test (Antibody And Igm Antibody)
146	LOM	Test, Hepatitis B (B Core, Be Antigen, Be Antibody, B Core Igm)
147	LQF	Dna-Reagents, Mycobacterium Spp.
148	LQG	Dna-Reagents, Mycoplasma Spp.
149	LQH	Dna-Reagents, Legionella
150	LQO	Dna-Reagents, Campylobacter Spp.
151	LRF	Candida Spp., Direct Antigen, Id
152	LRM	Anti-Dna Antibody (Enzyme-Labeled), Antigen, Control
153	LSK	Dna-Reagents, Chlamydia
154	LSL	Dna-Reagents, Neisseria
155	LSW	Anti-Dna Antibody, Antigen And Control
156	LTJ	Prostate-Specific Antigen (Psa) For Management Of Prostate Cancers
157	LTK	Test, Epithelial Ovarian Tumor-Associated Antigen (Ca125)
158	MAQ	Kit, Dna Detection, Human Papillomavirus
159	MBT	Dna-Probe, Reagent, Histoplasma Capsulatum
160	MCB	Antigen, C. Difficile
161	MCC	Dna-Probe, Haemophilus Spp.
162	MCD	Antigen, Ebv, Capsid
163	MCE	Respiratory Syncytial Virus - Elisa
164	MCS	Dna-Probe, Staphylococcus Aureus
165	MCT	Dna-Probe, Strep Pneumoniae
166	MDC	Dna-Probe - Blastomyces Dermatitidis
167	MDE	Dna-Probe, Reagents, Cryptococcal
168	MDF	Dna-Probe, Reagents, Coccidioides Immitis
169	MDK	Dna-Probe, Reagents, Streptococcal
170	MDU	Antigen, Elisa, Cryptococcus
171	MJB	Antigen, Cancer 549
172	MJH	Legionella, Spp., Elisa
173	MJK	Dna Probe, Trichomonas Vaginalis

174	MJM	Dna Probe, Gardnerella Vaginalis
175	MKT	Hepatitis Viral B Dna Detection
176	MKZ	Dna Probe, Nucleic Acid Amplification, Chlamydia
177	MLA	Dna Probe, Yeast
178	MTF	Total,Prostate Specific Antigen(Noncomplexed&Complexed) For Detection Of Prostate Cancer
179	MVC	System, Test, Her-2/Neu, Ihc
180	MVD	System, Test, Her-2/Neu, Nucleic Acid Or Serum
181	MXZ	Immunohistochemistry Assay,Antibody,Progesterone Receptor
182	MYA	Immunohistochemistry Antibody Assay, Estrogen Receptor
183	MYP	Test,Platelet Antibody
184	MYR	Test,Donor,Syphilis,Antigens,Treponemal
185	MZP	Assay,Hybridization And/Or Nucleic Acid Amplification For Detection Of Hepatitis C Rna,Hepatitis C Virus
186	NAF	Antigen(Complexed),Prostate Specific,(Cpsa)
187	NDZ	Assay, Nucleic Acid Amplification, Growth Identification, Mycobacterium Tuberculosis
188	NHS	Assay, Genotype, Hiv Drug Resistance, In Vitro
189	NHT	Assay, Nucleic Acid Amplification, Bacillus Anthracis
190	NID	Assay, Proliferation, In Vitro, T Lymphocyte
191	NIG	System, Test, Carbohydrate Antigen (Ca19-9), For Monitoring And Management Of Pancreatic Cancer
192	NIJ	System, Test, Genotypic Detection, Resistant Markers, Enterococcus Species
193	NIY	Autoantibodies, Anti-Soluble Liver Antigen (Sla), Autoimmune Hepatitis
194	NJR	Nucleic Acid Amplification Assay System, Group B Streptococcus, Direct Specimen Test
195	NJW	Control Material, Her-2/Neu, Immunohistochemistry
196	NKF	Immunohistochemistry Antibody Assay, C-Kit
197	NOM	Antigen, Galactomannan, Aspergillus Spp.
198	NOP	Elisa, Antibody, West Nile Virus
199	NPQ	Test, Factor V Leiden Mutations, Genomic Dna Pcr
200	NPR	Test, Factor Ii G20210a Mutations, Genomic Dna Pcr
201	NQD	Cardiac C-Reactive Protein, Antigen, Antiserum, And Control
202	NQF	Immunohistochemistry Assay, Antibody, Epidermal Growth Factor Receptor
203	NQX	System, Nucleic Acid Amplification Test, Dna, Methicillin Resistant Staphylococcus Aureus, Direct Specimen

204	NSD	Test, Fluorescence In Situ Hybridization (Fish), For Bladder Cancer Detection And Monitoring For Recurrence
205	NST	Autoantibodies, Acetylcholine Receptor, Acetylcholine Blocking And Non-Blocking
206	NTI	Drug Metabolizing Enzyme Genotyping Systems
207	NTM	Antigen, Inflammatory Response Marker, Sepsis
208	NTR	Immunohistochemical Reagent, Antibody (Monoclonal Or Polyclonal) To P63 Protein In Nucleus Of Prostatic Basal Cells
209	NUA	System, Cystic Fibrosis Transmembrane Conductance Regulator, Gene Mutation Detection
210	NXD	Nucleic Acid Amplification, Novel Influenza A Virus, A/H5 (Asian Lineage) Rna
211	NXG	Fluorescence In Situ Hybridization, Topoisomerase Ii Alpha, Gene Amplification And Deletion
212	NXO	Calprotectin, Fecal
213	NXX	Fish (Fluorescent In Situ Hybridization) Kit, Protein Nucleic Acid, Rna, Staphylococcus Aureus
214	NYI	Classifier, Prognostic, Recurrence Risk Assessment, Rna Gene Expression, Breast Cancer
215	NYO	Autoantibodies, Anti-Ribonucleic Acid Polymerase (Rnap) Iii Antibody
216	NYQ	Chromogenic In Situ Hybridisation, Nucleic Acid Amplification, Her2/Neu Gene, Breast Cancer
217	OAH	Fish (Fluorescent In Situ Hybridization) Kit, Protein Nucleic Acid, Enterococcus Faecalis
218	OAI	Assay, Enterovirus Nucleic Acid
219	OBE	Anti-Ss-A 52 Autoantibodies
220	OBW	11-Dehydro Thromboxane B2 Kit, Urinary
221	OBZ	Alpha-1-Antitrypsin Kit, Qualitative Phenotype
222	OCB	Rt-Pcr Multigene Expression Test, Sentinel Lymph Node, Cancer Metastasis Detection
223	OCN	Insulin Autoantibody Kit
224	ODV	Vitamin K Epoxide Reductase Complex Subunit One (Vkorc1) Genotyping System
225	ODW	Cytochrome P450 2c9 (Cyp450 2c9) Drug Metabolizing Enzyme Genotyping System
226	OEG	Autoantibodies, Skin (Bullous Pemphigoid 180 And Bullous Pemphigoid 230
227	OEH	Joint Biological Agent Identification And Diagnostic System (Jbaids) Tularemia Detection Kit
228	OEM	Human Metapneumovirus (Hmpv) Rna Assay System
229	OEP	Influenza A Virus Subtype Differentiation Nucleic Acid Assay
230	OIF	Tyrosine Phosphatase (Ia-2) Autoantibody Assay
231	OIU	Test, Epithelial Ovarian Tumor Associated Antigen (He4)
232	OIW	Software, Similarity Score Algorithm, Tissue Of Origin For Malignant Tumor Types
233	OKM	Antibodies, Outer-Membrane Proteins

234	OMG	Antisera, Fluorescent, Human Metapneumovirus
235	OMI	Multiplex Flow Immunoassay, T.Gondii, Rubella And Cmv.
236	OMM	Test 5, 10-Methylenetetrahydrofolate Reductase Mutations, Genomic Dna Pcr
237	OMN	C. Difficile Nucleic Acid Amplification Test Assay
238	OOU	Parainfluenza Multiplex Nucleic Acid Assay
239	OOX	Automated Occult Blood Analyzer
240	OPL	Multiplex Immunoassay For Measles Virus, Mumps Virus, Rubella And Varicella Zoster Virus
241	OPM	Multiplex Immunoassay For T. Gondii, Rubella, Cytomegalovirus And Herpes Simplex Virus 1 And 2
242	OPN	Auto-Antibodies; Phosphatidylserine, Prothrombin, Phosphatidylserine/Prothrombin Complex
243	OQO	Herpes Simplex Virus Nucleic Acid Amplification Assay
244	OQW	2009 H1n1 Influenza Virus (Swine Origin), Nucleic Acid Or Antigen, Detection And Identification
245	OSX	Galectin-3 In Vitro Diagnostic Assay
246	OTG	Non-Sars Coronavirus Multiplex Nucleic Acid Assay
247	OUY	Trichomonas Vaginalis Nucleic Acid Amplification Test System
248	OUZ	Nucleic Amplification Assays For The Detection Of Leishmania Nucleic Acids
249	OVF	Assay, Direct, Nucleic Acid Amplification, Q Fever
250	OVQ	Chronic Lymphocytic Leukemia Fish Probe Kit
251	OWD	Somatic Gene Mutation Detection System
252	OWE	Fluorescence In Situ Hybridization, Anaplastic Lymphoma Kinase, Gene Rearrangement
253	OWF	Immunohistochemical Assay, Helicobacter Pylori
254	OWK	Early Growth Response 1 (Egr) Fish Probe Kit
255	OWM	Prostate-Specific Antigen (Psa) For Prognostic, Recurrence Risk Assessment Of Prostate Cancers
256	OXP	Dna-Probe Kit, Human Chromosome X And Y, Bmt Engraftment
257	OYA	P2psa
258	OYB	Kit, Rna Detection, Human Papillomavirus
259	OYG	St2 Assay
260	OYM	Prostrate Cancer Genes Nucleic Acid Amplification Test System
261	OYP	Anti-Jcv Antibody Detection Assay
262	OYU	Dna-Probe Kit, Human Chromosome
263	OYZ	Group A Streptococcus Nucleic Acid Amplification Assay System

264	OZE	Influenza A And Influenza B Multiplex Nucleic Acid Assay
265	OZN	C.Difficile Toxin Gene Amplification Assay
266	OZX	Mycoplasma Pneumoniae Dna Assay System
267	OZY	Chlamydophila Pneumoniae Dna Assay System
268	OZZ	Bordetella Pertussis Dna Assay System
269	PAB	Cytomegalovirus (Cmv) Dna Quantitative Assay
270	PAF	Voltage Gated Calcium Channel (Vgcc) Antibody Assay
271	PBC	Manual Blood Grouping And Antibody Test Systems
272	PCG	21-Hydroxylase Antibody (21-Ohab)
273	PCL	Enzyme Linked Immunoabsorbent Assay, Rubeola Igm
274	PEO	Fungal Organisms, Nucleic Acid-Based Assay
275	PEU	System, Nucleic Acid-Based, Mycobacterium Tuberculosis Complex, Resistance Marker, Direct Specimen
276	PFG	Dna Fish Probe Kit For Specimen Characterization, Human Chromosome, Hematological Disorders
277	PFR	System, Cystic Fibrosis Transmembrane Conductance Regulator Gene, Mutations & Variants Panel Sequencing Detection
278	PFS	System, Cystic Fibrosis Transmembrane Conductance Regulator Gene, Variant Gene Sequence Detection
279	PGH	Hsv-1 And Hsv-2 Cns Nucleic-Acid Based Panel
280	PGI	Herpes Virus (Vzv, Hsv1, Hsv2), Dna Detection Assay For Cutaneous And Mucocutaneous Lesion Samples
281	PGX	Groups A, C And G Beta-Hemolytic Streptococcus Nucleic Acid Amplification System
282	PHJ	System, Mass Spectrometry, Multiplex Genotyping, Hereditary Thrombophilia Related Mutations
283	PHP	System, Colorectal Neoplasia, Dna Methylation And Hemoglobin Detection
284	PIT	Leishmania Spp. Antigen Detection Assay
285	PJG	Cancer-Related Germline Gene Mutation Detection System
286	PKW	Immunohistochemistry Assay, Antibody, Anaplastic Lymphoma Kinase
287	PLO	Meningitis/Encephalitis Pathogen Multiplex Nucleic Acid Detection System
288	PLS	Immunohistochemistry Assay, Antibody, Programmed Death-Ligand 1

Appendix 4: PC - Patent link

PC	Search String
CZS	ACLM/("Retinol binding protein" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
CZW	ACLM/("complement c3" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
DAB	ACLM/("Haptoglobin" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("Fluorescein isothiocyanate" or FITC))
DAD	ACLM/(Haptoglobin and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
DAH	ACLM/("gamma globulin" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
DAN	ACLM/("Fibrinopeptide" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
DAP	ACLM/("fibrinogen" or fibrin and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
DAT	ACLM/("fibrinogen" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and peroxidase)
DAZ	ACLM/("fibrinogen" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
DBE	ACLM/("smooth muscle" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "Indirect Immunofluorescence")
DBF	ACLM/(ferritin and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
DBL	ACLM/(autoantibodies and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "Indirect Immunofluorescence")
DBM	ACLM/(mitochondrial and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "Indirect Immunofluorescence")
DBT	ACLM/("Factor XIII" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
DCE	ACLM/(fab and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))

DCF	ACLM/(albumin and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
DCK	ACLM/("C-Reactive Protein" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("immunofluorescence" or "ELISA" or immunoassay OR "immune assay" or antigen))
DDB	ACLM/(Ceruloplasmin and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
DDC	ACLM/("Thyroglobulin" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
DDE	ACLM/("Carbonic Anhydrase" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
DDF	ACLM/("prothrombin" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
DDO	ACLM/(myoglobin and rhodamine and (diagnosis or identification or characterize or characterization or identify or determine or determining))
DDQ	ACLM/("Antithrombin iii" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
DDR	ACLM/("myoglobin" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
DDS	ACLM/(prealbumin and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("Fluorescein isothiocyanate" or FITC))
DDT	ACLM/("Macroglobulin" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
DDT	ACLM/("Macroglobulin" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and rhodamine)
DDX	ACLM/("Plasminogen" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (antiserum or antigen))
DDY	ACLM/("Macroglobulin" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
DDZ	ACLM/(albumin and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
DEA	ACLM/(myoglobin and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("Fluorescein isothiocyanate" or FITC))
DEB	ACLM/("Macroglobulin" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))

DEF	ACLM/(("fetuin" or AHSG or "Alpha-2-Hs-Glycoprotein") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay"))
DEG	ACLM/(Lactoferrin and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunoassay)
DEI	ACLM/("Alpha-1-Antitrypsin" or A1AT and (diagnosis or identification or characterize or characterization or identify or determine or determining) and FITC)
DEL	ACLM/("lipoprotein" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
DEM	ACLM/("Alpha-1-Antitrypsin" or A1AT and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or ELISA or immunoassay OR "immune assay"))
DER	ACLM/("Alpha-1-Lipoprotein" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and FITCH)
DFB	ACLM/("Alpha-1-Antitrypsin" or A1AT and (diagnosis or identification or characterize or characterization or identify or determine or determining) and rhodamine)
DFC	ACLM/(lipoprotein and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
DFF	ACLM/("Alpha-1-Antichymotrypsin" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
DFI	ACLM/("Spinal fluid" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
DFI	ACLM/("prostate specific antingen" or psa and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
DFJ	ACLM/(albumin and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
DGB	ACLM/("seminal fluid" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
DGI	ACLM/("breast milk" and rhodamine and (diagnosis or identification or characterize or characterization or identify or determine or determining))
DGJ	ACLM/("colostrum" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
DGX	ACLM/("ng1m" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))

DHF	ACLM/("Dkm" or km1 and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
DHI	ACLM/(ng3m and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
DHN	ACLM/(antinuclear and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "Indirect Immunofluorescence")
DHX	ACLM/(carcinoembrionic and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay" or antigen))
DHY	ACLM/(ng4m and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
DJB	ACLM/(digoxine and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (ria or radioimmunoassay))
DND	ACLM/(digoxine and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (ria or radioimmunoassay))
DNJ	ACLM/(digoxine and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (ria or radioimmunoassay))
DNL	ACLM/(digoxine and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (ria or radioimmunoassay))
DOA	ACLM/(digoxine and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (ria or radioimmunoassay))
DOE	ACLM/(digoxine and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (ria or radioimmunoassay))
DOG	ACLM/(digoxine and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (ria or radioimmunoassay))
DON	ACLM/(digoxine and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (ria or radioimmunoassay))
DOR	ACLM/(digoxine and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (ria or radioimmunoassay))
DOY	ACLM/(digoxine and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (ria or radioimmunoassay))
DPB	ACLM/(digoxine and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (ria or radioimmunoassay))

DPD	ACLM/(digoxine and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (ria or radioimmunoassay))
DPG	ACLM/(digitoxin and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "radioimmunoassay")
DPJ	ACLM/(amphetamine and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "radioimmunoassay")
DPO	ACLM/(digoxine and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (ria or radioimmunoassay))
GLZ	ACLM/(toxoplasma and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fixation or immunofixation))
GMG	ACLM/((coccidiodes or immitis) and agglutination and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay"))
GMI	ACLM/((("herpes virus" and (1 or 2))) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GMJ	ACLM/(histoplasma and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay" or antigen))
GMM	ACLM/(toxoplasma and (diagnosis or identification or characterize or characterization or identify or determine or determining) and agglutination)
GMN	ACLM/(Toxoplasma and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GMO	ACLM/((Entamoeba or Histolytica) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "Indirect Immunofluorescence")
GMQ	ACLM/(nontreponemal and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay" or antigen))
GMT	ACLM/(echovirus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and agglutination)
GMZ	ACLM/(("e.coli" or "escericchia") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay"))
GNC	ACLM/(salmonella and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "weil-felix")

GNE	ACLM/(cruzi and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "Indirect Immunofluorescence")
GNG	ACLM/(coxackie and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GNH	ACLM/((Schistosoma or Mansoni) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fluorescent or fluorescece))
GNJ	ACLM/(echovirus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and agglutination)
GNL	ACLM/(echovirus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GNT	ACLM/(adenovirus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and agglutination)
GNX	ACLM/(influenza and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GOB	ACLM/(adenovirus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and agglutination)
GOD	ACLM/(adenovirus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GOL	ACLM/(rubella and (diagnosis or identification or characterize or characterization or identify or determine or determining) and agglutination)
GON	ACLM/(rubella and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GOX	ACLM/(pertussis and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay" or antigen))
GPF	ACLM/(echinococcus and agglutination and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay"))
GPG	ACLM/((Trichinella or Spiralis) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "Indirect Immunofluorescence")
GPO	ACLM/(typhus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GPS	ACLM/("q fever" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))

GPW	ACLM/(psittacoccosis and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GQG	ACLM/(rsv or "respiratory syncytial virus" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GQH	ACLM/(cytomegalovirus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GQN	ACLM/((("herpes virus" and (1 or 2))) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GQR	ACLM/(parainfluenza and (diagnosis or identification or characterize or characterization or identify or determine or determining) and agglutination)
GQS	ACLM/(parainfluenza and (diaghttp://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearch-adv.htm&r=0&f=S&l=50&d=PTXT&Query=ACLM%2F%28parainfluenza+and+%28diagnosis+or+identification+or+characterize+or+characterization+or+identify+or+determine+or+determining%29+and+%28cf+or+%22complement+fixation%22%29%29nosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GQW	ACLM/(zoster and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GRC	ACLM/("Rubulavirus" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GRJ	ACLM/("Rubeola" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GRL	ACLM/(salmonella and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay" or antigen))
GRY	ACLM/(leptospira and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay" or antigen))
GSB	ACLM/mycoplasma and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
GSI	ACLM/(listeria and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "weil-felix")
GSL	ACLM/(francisella and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "weil-felix")

GSN	ACLM/("febrile antigen" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
GSO	ACLM/(agglutination and brucella and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay"))
GTY	ACLM/(streptococcus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay"))
JNL	ACLM/(Thyroglobulin and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunoassay)
JSS	ACLM/((Enterobacteriaceae) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
JSZ	ACLM/(pseudomonas and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
JWK	ACLM/(neoformans or cryptococcus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay"))
JWL	ACLM/(treponema and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "fta-abs")
JWT	ACLM/(aspergillus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
JWW	ACLM/(dermatitis and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (cf or "complement fixation"))
JZH	ACLM/("factor b" and (diagnosis or identification or characterize or characterization or identify or determine or determining))
JZO	Thyroid analyte detection and measurement
KHW	ACLM/((Entamoeba or Histolytica) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and agglutination)
KSZ	ACLM/((blood and type) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunoassay)
KTL	ACLM/("Anti-Dna" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fluotescence or "indirect immunofluorescence"))
KTS	ACLM/("gamma globulin" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay"))

LGB	ACLM/((gonococci or gonococcal) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunoassay)
LHK	ACLM/(candida and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay"))
LHL	ACLM/(legionella and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ((direct or indirect) and (fluorescence or fluorescent or immunofluorescent)))
LHT	ACLM/("Staphylococcus Aureus" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay" or antigen))
LIA	ACLM/(shigella and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay"))
LIG	ACLM/("intrinsic factor" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "radioimmunoassay")
LJN	ACLM/("epstein barr virus" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunofixation)
LIN	ACLM/(cytomegalovirus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (immunofluorescence OR ifa))
LIR	ACLM/(neisseria and (diagnosis or identification or characterize or characterization or identify or determine or determining) and elisa)
LJB	ACLM/(rubeola and (diagnosis or identification or characterize or characterization or identify or determine or determining) and elisa)
LJM	CLM/(antinuclear and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (eia or "enzyme immunoassay"))
LJO	ACLM/(cytomegalovirus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and agglutination)
LKJ	ACLM/(antinuclear and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (ifa or "immunofluorescent assay"))
LKO	ACLM/("anti rnp" or "anti-rnp" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
LKP	ACLM/("anti sm" or "anti-sm" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
LKQ	ACLM/("epstein barr virus" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunofixation)

LKT	ACLM/("Respiratory Syncytial Virus" or rsv and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (ifa or "immunofluorescent assay"))
LLH	ACLM/(clostridum and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunoassay)
LLL	ACLM/(antinuclear and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "enzyme-linked immunosorbant assay" or immunoassay OR "immune assay" or antigen))
LLM	ACLM/("epstein barr virus" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
LOL	ACLM/("hepatitis A" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunoassay)
LOM	ACLM/("hepatitis b" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (antigen))
LQF	ACLM/(Mycobacterium and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
LQG	ACLM/(mycoplasma and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
LQH	ACLM/(Legionella and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
LQO	ACLM/((Campylobacter) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction") andnot sars)
LRF	ACLM/(candida and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
LRM	ACLM/("Anti-Dna" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (EIA or "enzyme immunoassay"))
LSK	ACLM/((Chlamydia) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
LSL	ACLM/(neisseria and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
LSW	ACLM/("Anti-Dna" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
LTJ	ACLM/("prostate specific antigen" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))

LTK	ACLM/("Epithelial Ovarian Tumor-Associated Antigen" or ca125 and (diagnosis or identification or characterize or characterization or identify or determine or determining) and elisa)
	ACLM/(("Human Papillomavirus" or HPV) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
MBT	ACLM/(Histoplasma and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
MCB	ACLM/(clostridium and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
MCC	ACLM/(haemophilus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
MCD	ACLM/("epstein barr virus" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
MCE	ACLM/("Respiratory Syncytial Virus" or rsv and (diagnosis or identification or characterize or characterization or identify or determine or determining) and elisa)
MCS	ACLM/("Staphylococcus Aureus" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
MCT	ACLM/(Pneumoniae and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
MDC	ACLM/((Blastomyces or "B.Dermatitidis") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
MDE	ACLM/(Cryptococc$ and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
MDF	ACLM/((Coccidioides or "C.Immitis") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
MDK	ACLM/(Streptococc$ and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
MDU	ACLM/(cryptococcus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and elisa)
MJB	ACLM/("cancer 549"and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
MJH	ACLM/(legionella and (diagnosis or identification or characterize or characterization or identify or determine or determining) and elisa)
MJK	ACLM/((Trichomonas or "T.Vaginalis") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))

MJM	ACLM/((Gardnerella or "G.Vaginalis") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
MKT	ACLM/(("hepatitis b") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
MKZ	ACLM/((Chlamydia) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
MLA	ACLM/(yeast and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
MTF	ACLM/("prostate specific antigen" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
MVC	ACLM/((her2 or neu) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (immunohistochemistry or ihc))
MVD	ACLM/((her2 or neu) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
MXZ	ACLM/(("Progesterone receptor" or NR3C3) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (immunohistochemistry or ihc))
MYA	ACLM/(("estrogen receptor" or ers) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (immunohistochemistry or ihc))
MYP	ACLM/(platelet and (diagnosis or identification or characterize or characterization or identify or determine or determining) and elisa)
MYR	ACLM/(syphilis and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
MZP	ACLM/("Hepatitis C" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
NAF	ACLM/("prostate specific antigen" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
NDZ	ACLM/(Mycobacterium and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
NHS	ACLM/("HIV" and "drug resistance" and (diagnosis or identification or characterize or characterization or identify or determine or determining))
NHT	ACLM/((anthracis) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
NID	ACLM/("T lymphocyte" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunoassay)

NIG	ACLM/("ca19-9" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunoassay)
NIJ	ACLM/((enterococcus and ("drug resistent" or resistance)) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
NIY	ACLM/("Soluble Liver Antigen" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and elisa)
NJR	ACLM/("Streptococcus" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
NJW	ACLM/((her2 or neu) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (immunohistochemistry or ihc))
NKF	ACLM/((c-kit) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (immunohistochemistry or ihc))
NOM	ACLM/(aspergillus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "sandwich elisa")
NOP	ACLM/("West Nile Virus" or WN and (diagnosis or identification or characterize or characterization or identify or determine or determining) and elisa)
NPQ	ACLM/((Thrombophilia) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and mutation)
NPR	ACLM/((Thrombophilia) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and mutation)
NQD	ACLM/("C-Reactive Protein" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("immunofluorescence" or "ELISA" or immunoassay OR "immune assay" or antigen))
NQF	ACLM/(("Epidermal Growth Factor Receptor" or EGFR) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (immunohistochemistry or ihc))
NQX	ACLM/("Staphylococcus Aureus" and (Resistant or "drug resistance") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
NSD	ACLM/("bladder cancer" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
NST	ACLM/(("Acetylcholine Receptor" or AChR) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (immunohistochemistry or ihc))
NTI	ACLM/((diagnosis or identification or characterize or characterization or identify or determine or determining) and (mutation or genotype or polymorphism)) AND Spec/("drug metabolizing enzyme")
NTM	ACLM/(sepsi and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunoassay)

NTR	ACLM/((TP63 or P63) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (immunohistochemistry or ihc))
NUA	ACLM/("cystic fibrosis" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (mutation or genotype or polymorphism))
NXD	ACLM/("influenza AH5" or (influenza and "asian lineage") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
NXG	ACLM/(("Topoisomerase ii Alpha" or top2a) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
NXO	ACLM/(calprotectin and (diagnosis or identification or characterize or characterization or identify or determine or determining) and elisa)
NXX	ACLM/("Staphylococcus Aureus" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (FISH or "fluorescent in situ hybridization" or hybridization))
NYI	ACLM/("breast cancer" and "gene expression" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (mutation or genotype or polymorphism))
NYO	ACLM/("Anti-Ribonucleic Acid Polymerase" or Rnap and (diagnosis or identification or characterize or characterization or identify or determine or determining) and elisa)
NYQ	ACLM/(("breast cancer" or "Her2" or "Neu" or Her2neu) and (CISH or "Chromogenic In Situ Hybridisation") and (diagnosis or identification or characterize or characterization or identify or determine or determining))
OAH	ACLM/(Enterococcus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (FISH or "fluorescent in situ hybridization" or hybridization))
OAI	ACLM/(enterovirus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OBE	ACLM/("Ss-A 52" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunoassay)
OBW	ACLM/("11-Dehydro Thromboxane" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ELISA))
OBZ	ACLM/("Alpha-1-Antitrypsin" or A1AT and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunoassay)
OCB	ACLM/("Sentinel Lymph Node" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OCN	ACLM/(insulin and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunoassay)
ODV	ACLM/(("Vitamin K Epoxide Reductase" or "vkorc1" or "vkorc") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (mutation or genotype))

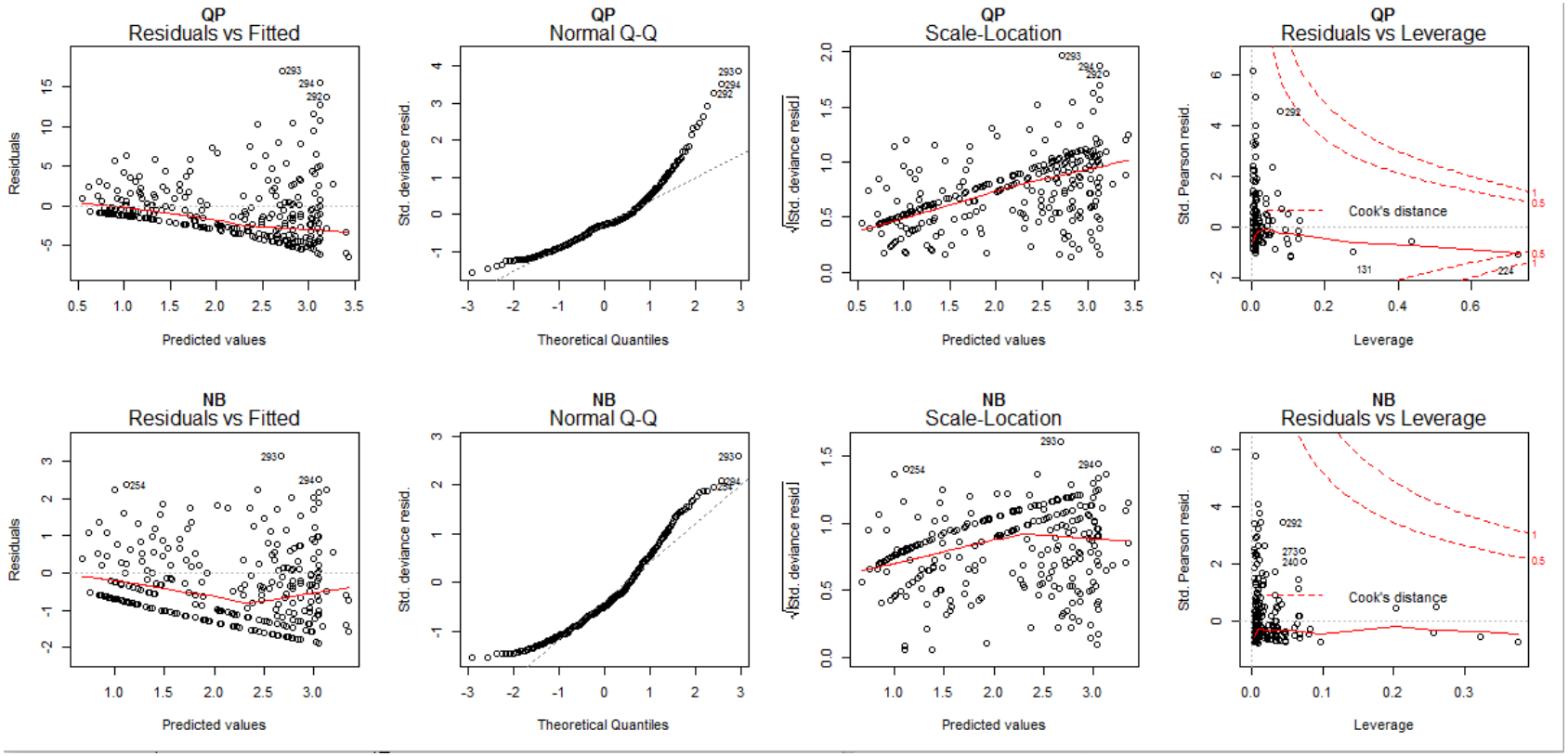
ODW	ACLM/(("cyp450 2c9" or "Cytochrome P450 2c9") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (mutation or genotype or polymorphism))
OEG	ACLM/("Bullous Pemphigoid" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
OEH	ACLM/(Tularemia and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OEM	ACLM/("Human Metapneumovirus" or hmpv and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OEP	ACLM/("influenza A" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OIF	ACLM/(("Tyrosine Phosphatase" or Ia-2) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "radioimmunoassay")
OIU	ACLM/(he4 and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "sandwich elisa")
OIW	ACLM/((cancer or tumor) and "tissue of origin" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (mutation or genotype or polymorphism))
OKM	ACLM/("Outer-Membrane Proteins" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ELISA))
OMG	ACLM/(Metapneumovirus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
OMM	ACLM/((Thrombophilia) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and mutation")
OMN	ACLM/(clostridium and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OOU	ACLM/((parainfluenza) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OOX	ACLM/("occulte blood" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunoassay)
OPL	ACLM/((measles or rubella or mumps or zoster) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "flow immunoassay")
OPM	ACLM/((Gondii or Rubella or Cytomegalovirus or "Herpes Simplex Virus" or hsv) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "flow immunoassay")
OPN	ACLM/((Phosphatidylserine or Prothrombin) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and elisa)

OQO	ACLM/(("Herpes Simplex") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OQW	ACLM/(h1n1 and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OSX	ACLM/(galectin and (diagnosis or identification or characterize or characterization or identify or determine or determining) and elisa)
OTG	ACLM/(("corona virus" or "coronaviridae") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction") andnot sars)
OUY	ACLM/(streptococcus and hemolytic and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OUZ	ACLM/(Leishmania and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OVF	ACLM/(("q fever" or "Coxiella burnetii" or "coxiella") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OVQ	ACLM/(("Chronic Lymphocytic Leukemia" or CLL) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
OWD	ACLM/("Somatic gene mutation" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OWE	ACLM/(("Anaplastic Lymphoma Kinase" or ALK) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (FISH or "fluorescent in situ hybridization" or hybridization))
OWF	ACLM/(Pylori and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (immunohistochemistry or ihc))
OWK	ACLM/(("Early Growth Response 1 " or egr1 or egr-1) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
OXP	ACLM/((chromosome and human and (x or y or sexual)) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
OYA	ACLM/(p2psa and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (eia or "enzyme immunoassay"))
OYB	ACLM/(("Human Papillomavirus" or HPV) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OYG	ACLM/(st2 and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "sandwich ELISA")
OYM	ACLM/("Prostate cancer" and "nucleic acid amplification" and (diagnosis or identification or characterize or characterization or identify or determine or determining))

OYP	ACLM/(jcv or "John Cunningham virus" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and elisa)
OYU	ACLM/((chromosome and human) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
OYZ	ACLM/(streptococcus and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OZE	ACLM/(("influenza A" or "influenza b") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OZN	ACLM/((Clostridium and toxin and gene) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction") andnot sars)
OZX	ACLM/("mycoplasma pneumoniae" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OZY	ACLM/((Chlamydophila or chlamidya) and Pneumoniae and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
OZZ	ACLM/((pertussis) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
PAB	ACLM/((Cytomegalovirus or cmv) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
PAF	ACLM/(("Voltage Gated Calcium Channel" or Vgcc) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and "radioimmunoassay")
PBC	ACLM/((blood and type) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and immunoassay)
PCG	ACLM/("Hydroxylase" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and radioimmunoassay)
PCL	ACLM/(rubeola and (diagnosis or identification or characterize or characterization or identify or determine or determining) and elisa)
PEO	ACLM/((fungus or "fungal organism") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
PEU	ACLM/((((("corona virus" OR "coronaviridae") AND ((((((diagnosis OR identification) OR characterize) OR characterization) OR identify) OR determine) OR determining)) AND (("nucleic acid amplification" OR PCR) OR "polymerase reaction")) ANDNOT sars)
PFG	ACLM/((hematology) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (fish or "fluorescent in-situ hybridization"))
PFR	ACLM/("cystic fibrosis" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (mutation or genotype or polymorphism))

PFS	ACLM/("cystic fibrosis" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (mutation or genotype or polymorphism))
PGH	ACLM/("herpes simplex" and (1 or 2) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
PGI	ACLM/(("Herpes Simplex") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
PGX	ACLM/(streptococcus and hemolytic and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
PHJ	ACLM/((diagnosis or identification or characterize or characterization or identify or determine or determining) and (mutation or genotype or polymorphism)) AND Spec/("drug metabolizing enzyme")
PHP	ACLM/("Colon cancer" and methylation and (diagnosis or identification or characterize or characterization or identify or determine or determining))
PIT	ACLM/(leishmania and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay OR "immune assay" or antigen))
PJG	ACLM/(("Cancer Related Germline" or germline or "cancer-germline") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (genotyping or microarray or sequencing))
PKW	ACLM/((ALK or " Anaplastic Lymphoma Kinase") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (immunohistochemistry or ihc))
PLO	ACLM/((meningitis or encephalitis) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("nucleic acid amplification" or PCR or "polymerase reaction"))
PLS	ACLM/((PD-L1 or pdl1 or " Programmed Death-Ligand 1") and (diagnosis or identification or characterize or characterization or identify or determine or determining) and (immunohistochemistry or ihc))
OWM	ACLM/("prostate specific antigen" and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))
OMI	ACLM/(Gondi and Rubella and (CMV or Cytomegalovirus) and (diagnosis or identification or characterize or characterization or identify or determine or determining) and ("radio-immune assay" or "immunofluorescence assay" or "ELISA" or immunoassay))

Appendix 5: QP and NB Diagnostic graphs on number of incremental innovations



Appendix 6: Diagnostic plots of NB returning statistically significant results

This appendix reports plots that were used to check that the assumption of the NB were respected, no plot suggested that the assumptions were not respected.

This appendix reports also the VIF for each model. The VIF is calculated on the models and returns an estimate of the extent to which the variance of the regression coefficient is increased by correlation in comparison to non-linearly correlated values (Minitab, 2016). A VIF value of 1 indicate

that there is no correlation, a value between 1 and 5 indicates a moderate correlation and a value of 5 or higher indicate high correlation. (Minitab, 2016). The highest VIF was 1.44.

Incremental innovation

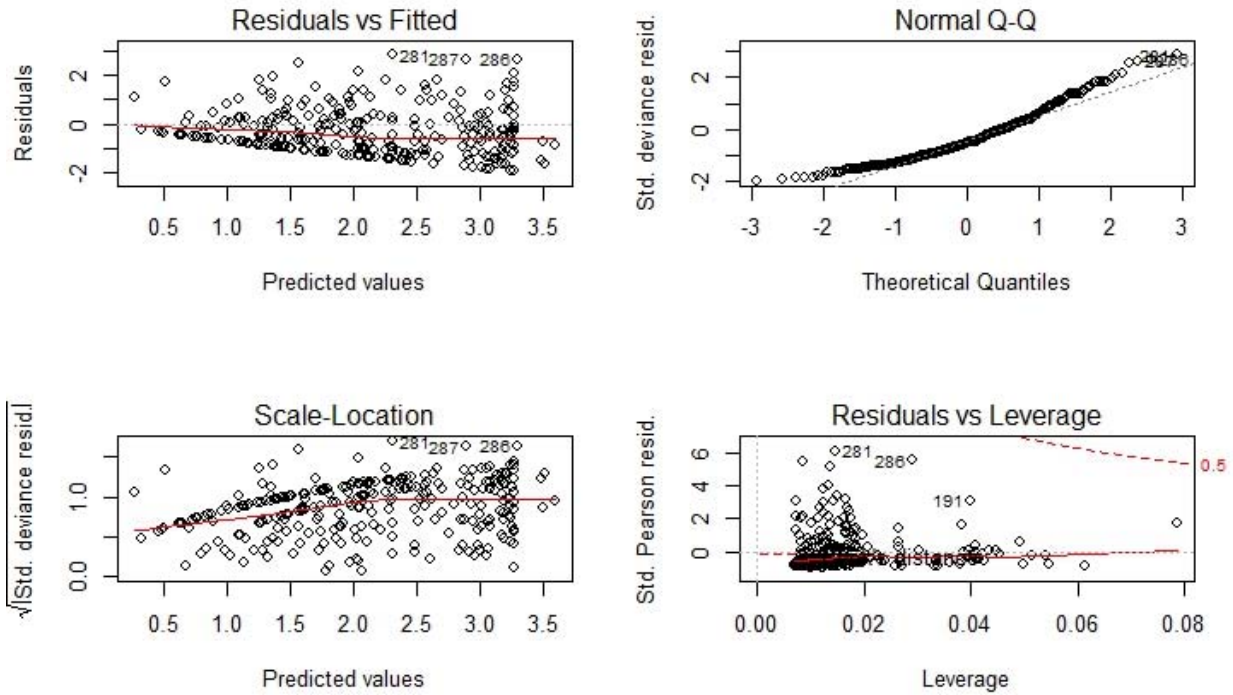


Figure 7 Diagnostic plots of model 3: Incremental innovation ~ DNA

Incremental innovation ~ DNA

```
     Age ProductRequirements2 ProductRequirements3          DNAorNOTDNA
1.511792             1.227479             1.290257             1.440999
```

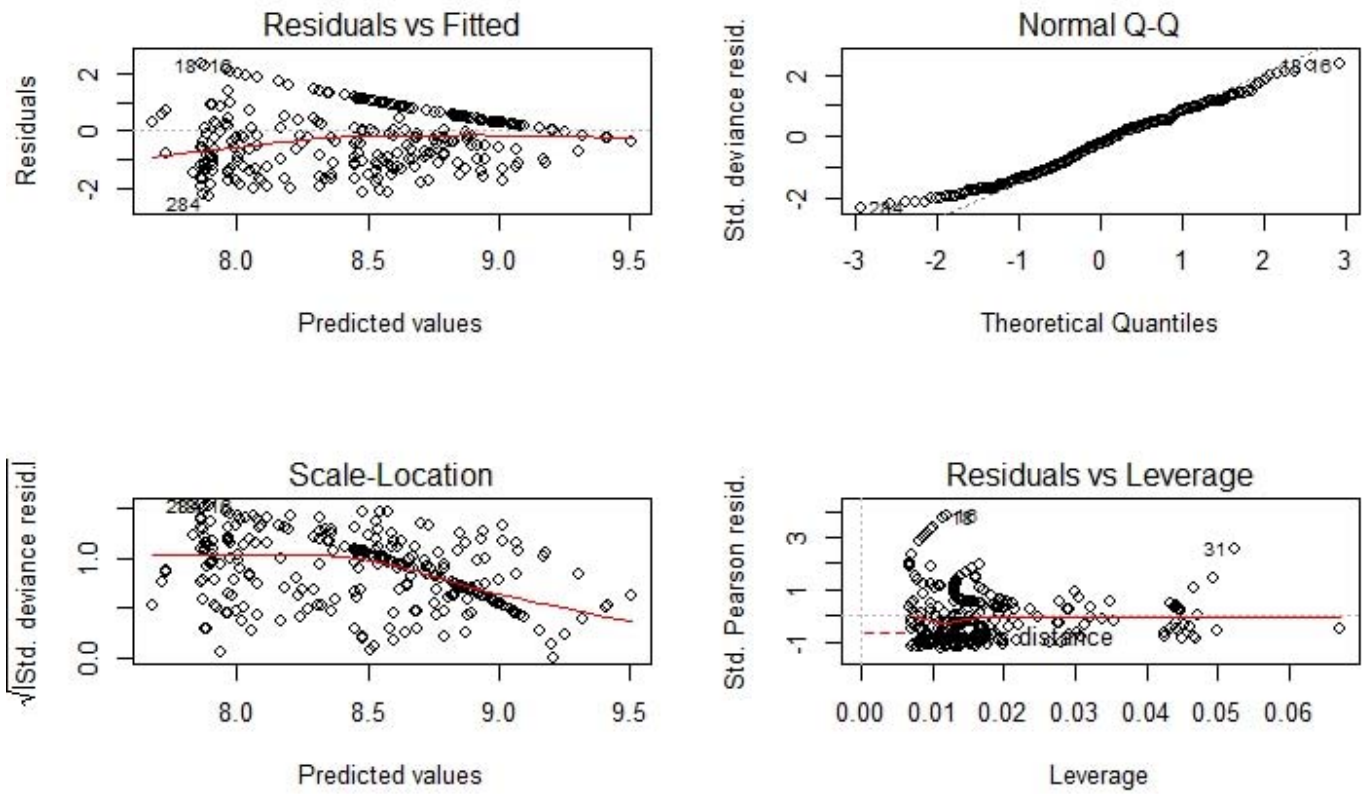


Figure 8 Diagnostic plot of model 4: Incremental innovation ~ Presence of patents

Incremental innovation ~ Presence of patents

```
                Age ProductRequirements2 ProductRequirements3 PresenceOfPatentsYES
           1.289041             1.225182             1.298301             1.242319
```

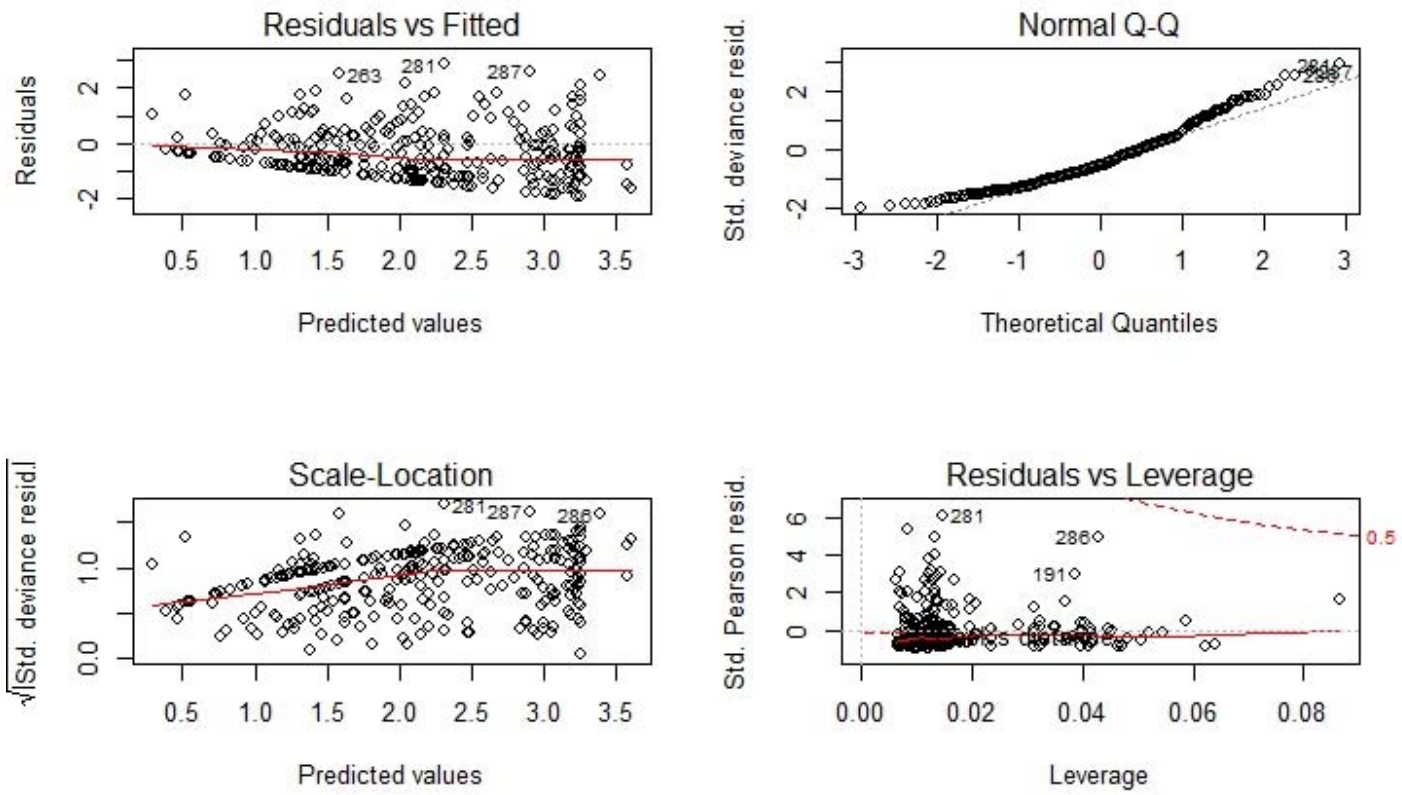


Figure 9 Diagnostic plot of model 5: incremental innovation ~ Private ownership

Incremental innovation ~ Private ownership

```
             Age ProductRequirements2 ProductRequirements3       PrivateIPRatio
        1.155195             1.221679             1.310984             1.113038
```

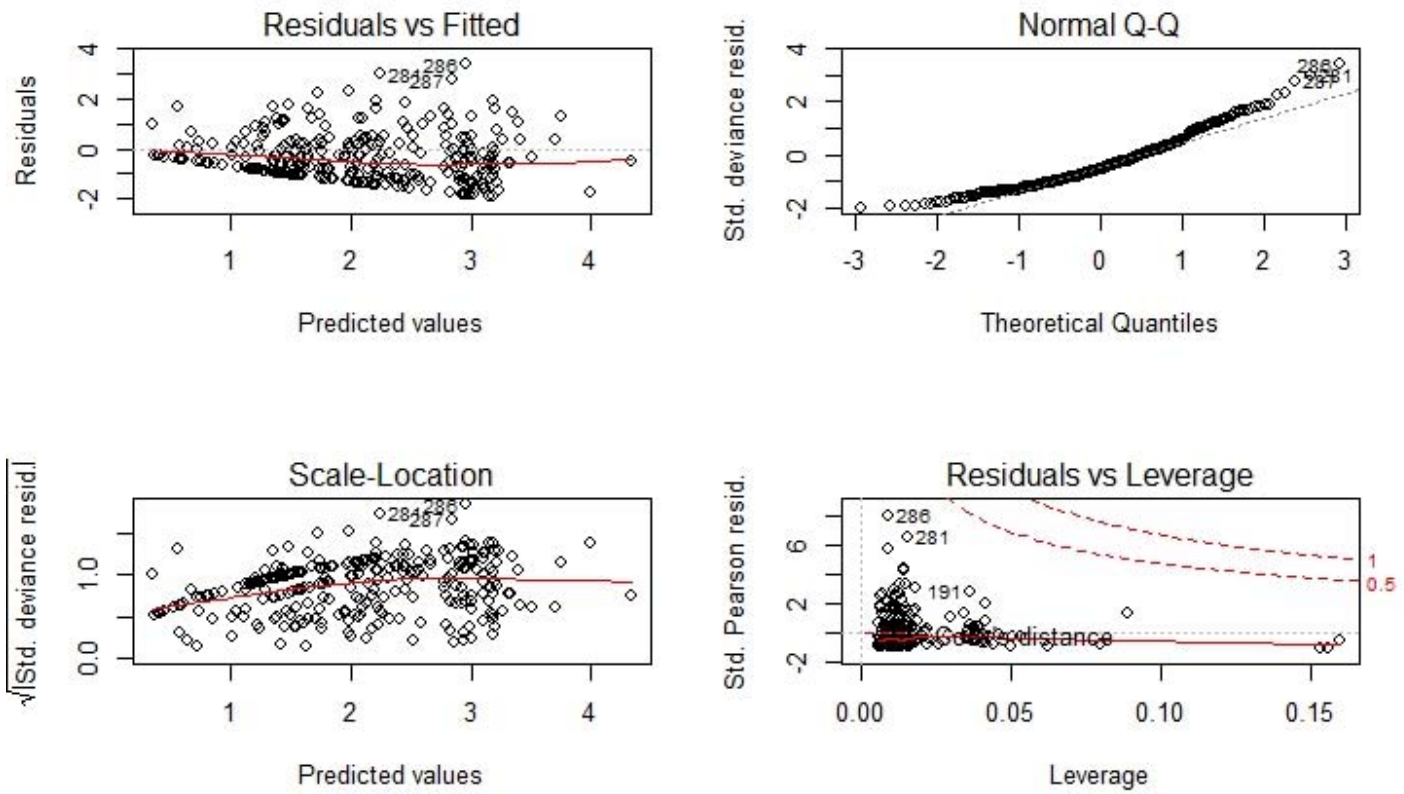


Figure 10 Diagnostic plot of model 8: Incremental innovation~ Collaborations

Incremental innovation~ Collaborations

```
                Age   ProductRequirements2   ProductRequirements3 NumberOfCollaborations
           1.085967               1.213088               1.283838               1.003308
```

Strength of monopoly

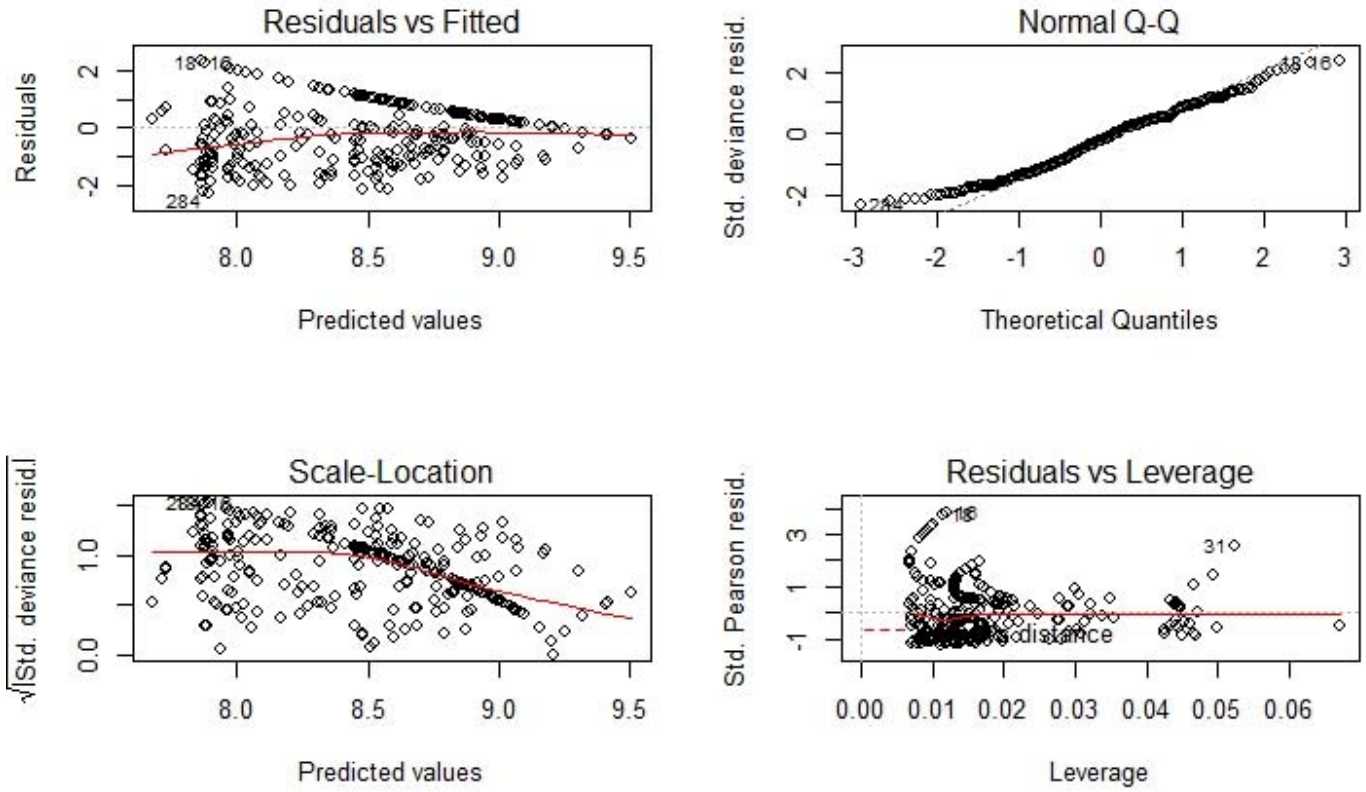


Figure 11 Diagnostic plot of model 4: Strength of monopoly ~ Presence of patents

Strength of monopoly ~ Presence of patents

```
                Age ProductRequirements2 ProductRequirements3 PresenceOfPatentsYES
           1.292395             1.249371             1.339210             1.230897
```

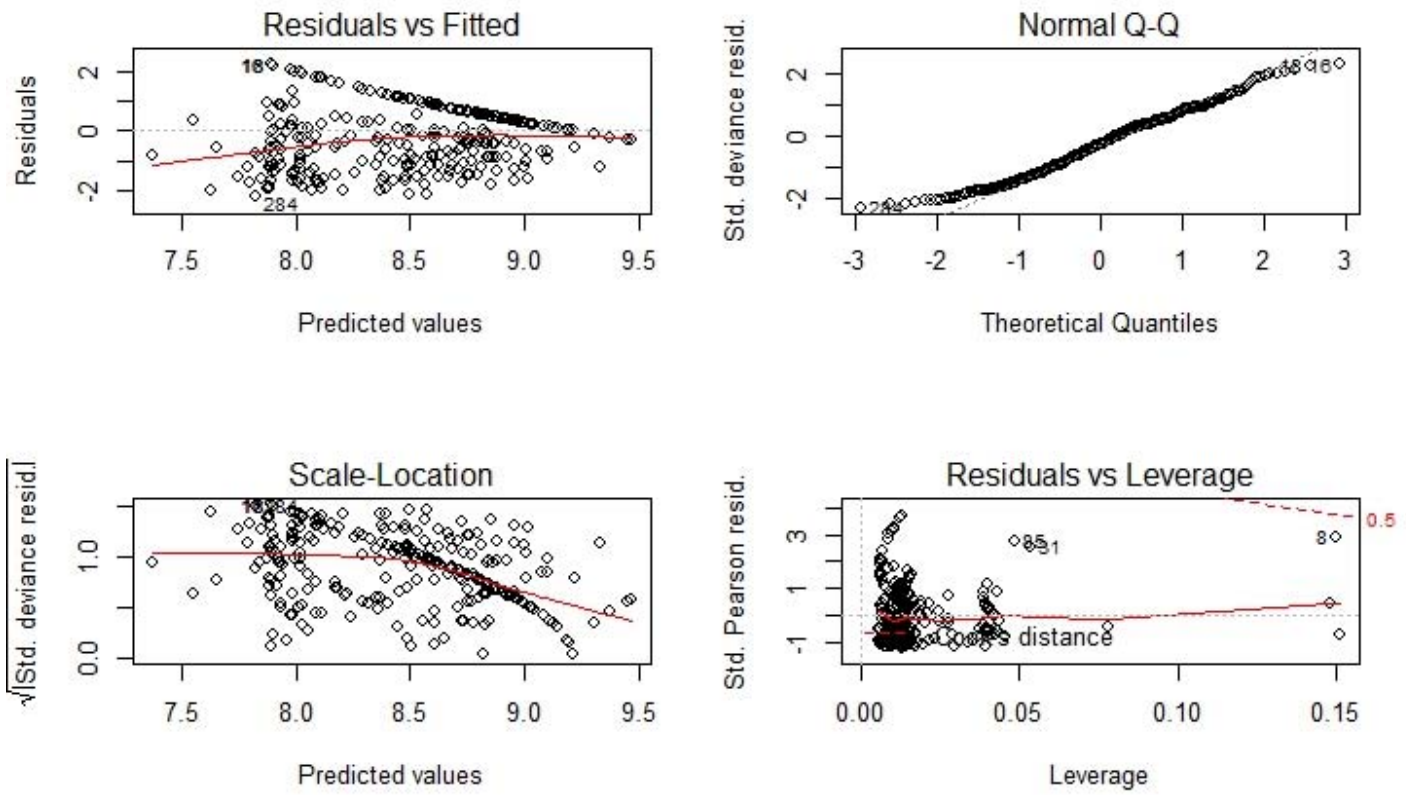


Figure 12Diagnostic plot of model 8: Strength of monopoly ~ Collaborations

Strength of monopoly ~ Collaborations

```
                 Age   ProductRequirements2   ProductRequirements3 NumberOfCollaborations
            1.100834               1.239575               1.329710               1.003085
```

Appendix 7: Proportional hazard assumption tests and VIF of models returning statistically significant values

A test on the global model returning a P value lower than 0.05 indicates that there the proportional hazard assumption was violated.

The VIF is calculated on the models and returns an estimate of the extent to which the variance of the regression coefficient is increased by correlation in comparison to non-linearly correlated values (Minitab, 2016). A VIF value of 1 indicate that there is no correlation, a value between 1 and 5 indicates a moderate correlation and a value of 5 or higher indicate high correlation. (Minitab, 2016). The largest VIF was 1.29.

Barrier of entry ~ Presence of patents

```
                              rho      chisq         p
ProductRequirements2 -0.162935410 4.81473577 0.0282174
ProductRequirements3 -0.009338708 0.01718432 0.8957049
PresenceOfPatentsYES  0.050532601 0.50374204 0.4778605
GLOBAL                         NA 6.20298930 0.1021413

VIF
ProductRequirements2 ProductRequirements3 PresenceOfPatentsYES
            1.219602             1.285278             1.060125
```

Barrier of entry ~ Number of IP rights

```
                             rho      chisq          p
ProductRequirements2 -0.16757141 5.11570340 0.02371025
ProductRequirements3 -0.01299469 0.03210677 0.85779352
NumberOfIPRights      0.02008455 0.12128872 0.72764095
GLOBAL                       NA 6.08831818 0.10739153

VIF
ProductRequirements2 ProductRequirements3     NumberOfIPRights
            1.212264             1.251840             1.041987
```

Barrier of entry ~ Private IP ratio

```
                              rho      chisq          p
ProductRequirements2 -0.161252925 4.71471710 0.02990549
ProductRequirements3 -0.008242751 0.01340591 0.90782382
PrivateIPRatio        0.033346577 0.24344030 0.62173232
GLOBAL                         NA 5.89195007 0.11698707

VIF
ProductRequirements2 ProductRequirements3       PrivateIPRatio
            1.214625             1.280554             1.061196
```

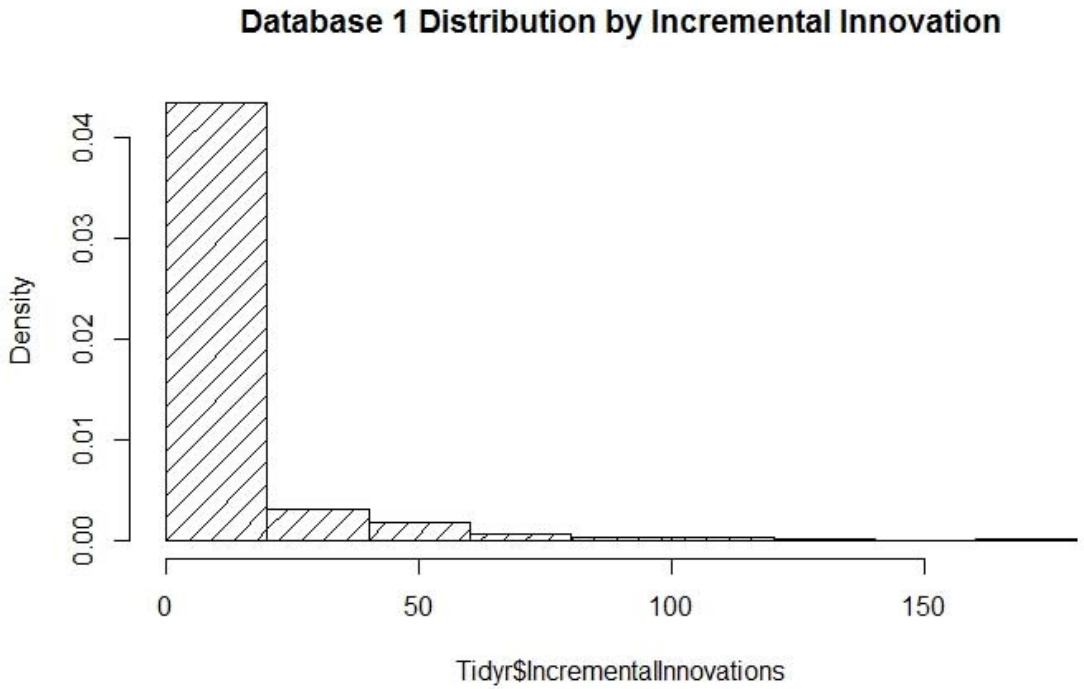
Barrier of entry ~ Number of IP holders

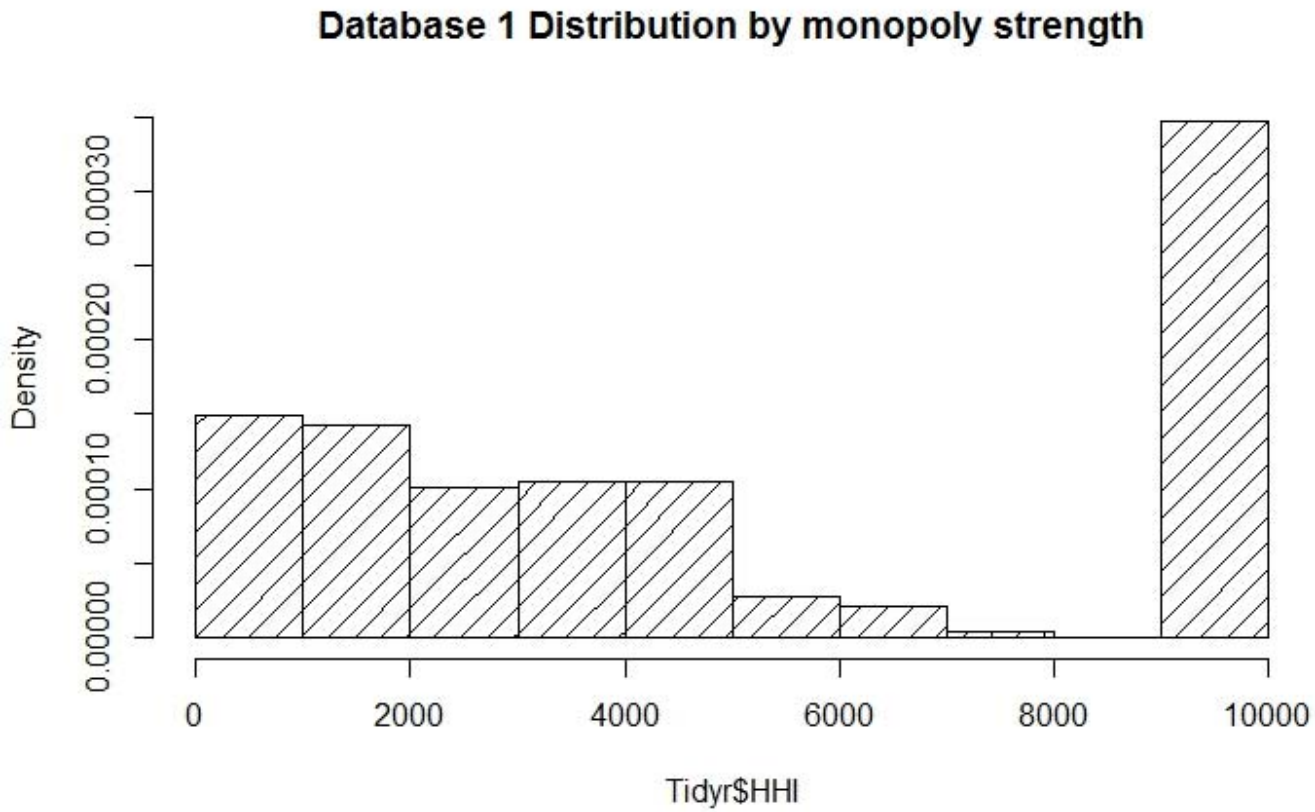
```
                             rho      chisq          p
ProductRequirements2 -0.16586874 5.01311585 0.02515599
ProductRequirements3 -0.01206578 0.02738419 0.86856486
NumberOfIPHolders     0.01771843 0.09213393 0.76148164
GLOBAL                        NA 5.93843670 0.11464413

VIF
ProductRequirements2 ProductRequirements3    NumberOfIPHolders
            1.212469             1.243743             1.033764
```

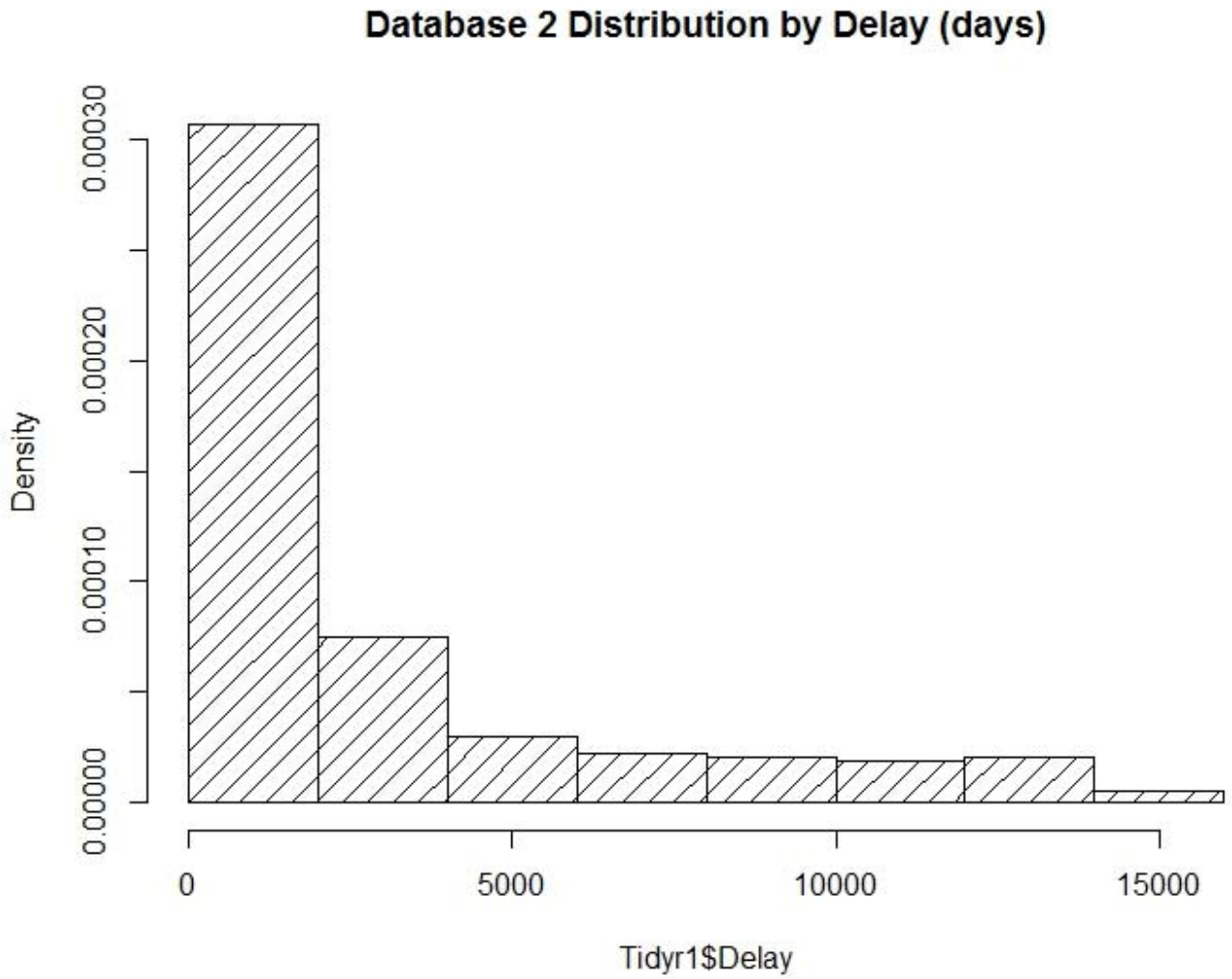
Barrier of entry ~ Number of collaborations

```
                               rho      chisq          p
ProductRequirements2   -0.16629862 5.04063264 0.02475945
ProductRequirements3   -0.02069476 0.07988051 0.77745941
NumberOfCollaborations  0.05775856 0.83699095 0.36025878
GLOBAL                          NA 6.72307339 0.08126821

VIF
ProductRequirements2   ProductRequirements3 NumberOfCollaborations
            1.212359               1.241703               1.032406
```

Appendix 8: Additional descriptive statistics




Database 1 Distribution by monopoly strength
Density
0.00000
0.00010
0.00020
0.00030
0
2000
4000
6000
8000
10000
Tidyr$HHI


Database 2 Distribution by Delay (days)
Density
0.00000
0.00010
0.00020
0.00030
0
5000
10000
15000
Tidyr1$Delay