Understanding the Conditions for which Rare Cancers are Successfully Treated with Therapeutics: Insights From QCA

Philippa Crane
University of Sussex
SPRU
pc61@sussex.ac.uk

Abstract

Understanding the Conditions for which Rare Cancers are Successfully Treated with Therapeutics: Insights from QCA

The research project summarised here will inform both policy and industry by identifying socio-technical conditions that lead to successful drug innovation. Motivation for this research stems from the question of why drugs for certain diseases are developed while other potential projects are not advanced, the answer to which is commonly perceived to be market failure. By focusing on the development of drugs for rare diseases (and in particular rare cancers), this research will also contribute towards understanding of dynamics of innovation in the emerging field of personalised medicine (Boon and Moors, 2008). The research questions to be addressed are: 1) What conditions of rare cancers contribute towards their successful treatment with therapeutics? 2) Assuming a complex web of interactions exists, what combinations of these causal conditions determine successful treatment of rare cancers?

The theoretical contribution of this research is located at the intersection of evolutionary economics and sociology, both of which contribute to the conceptualisation of different types of conditions that effect drug innovation. Concepts from evolutionary economics inform the discussion by highlighting the importance of market demand, scientific and technological knowledge and the system infrastructure surrounding innovations (Schmookler, 1966, Nelson and Winter, 1982, Freeman, 1995, Nelson, 2011). These institutional factors are complemented by the sociological literature which highlights the influence of social framing and expectations on the development of innovation, important for dimensions such as predictions of market size (Gelijns and Rosenberg, 1994, Epstein, 1995, Borup et al., 2006, Davis and Abraham, 2010).

The literature gap to be addressed is two-fold; firstly, in its theoretical contribution, the research will inform the discussion of the drivers of innovation and the interaction(s) between different causal conditions; secondly, in empirical terms, the research aims to counter the commonly perceived market failure argument in explaining the lack of...
therapeutics produced for diseases that affect small populations. This is necessary in light of the current policy initiatives, such as advanced market commitments and orphan drug legislation, which are reliant on the emphasis of market demand in defining drug innovation.

The methodology that will be implemented to achieve the goals of the research is Qualitative Comparative Analysis (QCA). This method allows for a number (between 10 and 200) of case studies to be compared in line with their membership into pre-determined conditions (as set out by the theoretical literature review above). The method, using set theory and Boolean algebra to compare cases, produces an overall picture of the necessary and sufficient conditions contributing towards an outcome (in this case successful production of therapeutic drugs). This methodology will allow the present research to provide a new perspective on the conditions influencing the drug development process and therefore provide an insight into ways in which these conditions can be manipulated to facilitate innovation in different directions.

References:
UNDERSTANDING THE CONDITIONS UNDER WHICH RARE CANCERS ARE SUCCESSFULLY TREATED WITH THERAPEUTICS: INSIGHTS FROM QCA

This paper presents the first stage of a research project that aims to inform both policy and industry by identifying patterns of behaviour and the underlying socio-technical conditions associated with improved success in the treatment of a subset of cancers, specifically those affecting small populations (herein, ‘rare cancers’).

A common explanation for the absence of therapeutics for rare diseases is market failure (Pablos-Mendez et al., 1999, Chataway et al., 2010, Fehr et al., 2011). ‘Market failure’ is perceived when there is no commercial incentive for the private sector to invest in innovative activities due to the prospect of small returns, theoretically stimulating the requirement for policy intervention (Nelson, 2011). The main policy for rare diseases, the Orphan Drug Act (ODA)\(^1\), aims to incentivise private sector research and development (R&D) despite market failure. Incentives include: grant funding opportunities, tax credits, increased period of market exclusivity and interaction with regulatory bodies (web 1, web 2). These policies have also led to a formal definition of rare diseases. In the EU rare diseases are defined as those affecting less than 1 in 2000 people in the European population (web 3), whereas in the USA the ratio is roughly 1:1570 (web 4). There are an estimated 7,000 rare diseases indicating that a substantial global health burden exists, with many millions of people affected (web 3). Rare diseases is a useful lens to perceive different types of cancers, where it is increasingly common for cancer groups to be split into subtypes according to differing characteristics (Curtis et al., 2012).

The first motivation for this research relates to a lack of therapeutics available to treat a number of diseases. Despite substantial variation within rare diseases, the majority remain untreated; where only 200 (2.8%) of the estimated 7,000 conditions have been addressed (Weinstein, 2012). In light of the changing technological paradigm in therapeutics, towards rational drug design, it is clear that decisions determining innovation and the diseases addressed innovation have become more deliberate (Mazzucato and Dosi, 2006, Hopkins et al., 2007). Accordingly this study will investigate the particular characteristics of diseases that influence their successful treatment with drug therapies. In particular, there exists a large inequality between well treated and relatively untreated cancers (Nelson, 2008).

\(^1\) Introduction of ODA in USA was 1983 and in EU, 2001.
Further motivation for this research comes from its broader application to the area of personalised medicine\(^2\), where the small potential markets in personalised medicine makes it analogous to rare diseases (Boon and Moors, 2008). Furthermore, increasing knowledge of genomics is motivating the ‘splitting’ of diseases into smaller categories (Hedgecoe, 2003, Curtis et al., 2012). Resulting patterns in the industry has shown a shift from blockbusters to ‘niche busters’ (Dolgin, 2010). This, coupled with the low productivity of the industry (Munos, 2009, Pammolli et al., 2011), illustrates the saliency of the conclusions drawn from this research.

**THEORETICAL LITERATURE**

The main theoretical literatures to be applied in this study are evolutionary economics and the sociology of science and technology. Each literature will contribute towards building a list of the conditions which play a role in driving innovation. In broad terms evolutionary economics highlights the importance of a combination of market demand, the amount and type of scientific and technological knowledge and the involvement and interactions between relevant organisations. However, the evolutionary economics perspective does not sufficiently address the socio-cultural embeddedness of these processes, motivating the inclusion of the sociology of science and technology which introduces a more context-dependent representation.

Early discussions surrounding the question of which forces determine innovation began with the ‘science push’ model. This purported that the sole requirement to progress technological change, and therefore economic development, was the input of resources into the science base (Bush, 1945). However, critics highlighted the lack of generalisability of the model, as it did not account for cases where technological advances preceded scientific knowledge (Nelson, 2008). Consequently, market demand was suggested as an alternative driver of innovation (Schmookler, 1966, Rothwell et al., 1974). However, this too was criticised due to the definitional and methodological difficulties of the papers commonly used to support it (Mowery and Rosenberg, 1979).

In response to these inadequacies, a school of economic thought emerged emphasising the dynamic nature of innovation as a consequence of a complex web of interdependencies between various factors. This evolutionary perspective is associated with two groundbreaking publications from 1982 (Dosi, 1982, Nelson and Winter, 1982). One specifically addresses the question - “why [do] certain technological developments emerge

---

\(^2\) Personalised medicine is a fast-growing stream of medicine which involves adapting therapies in line with a patients’ genetic makeup.
and not others?” (Dosi, 1982:148). The answer is suggested to be the complex nature of the interactions between technological trajectories and environmental selection pressures which influence the evolution of innovations (1982). Such selection pressures include scientific advances, economics, institutional variables and unresolved difficulties in previous paradigms (ibid). The second publication details the dynamic nature of change and the organisational attributes on which selection pressures act (Nelson and Winter, 1982).

One subsequent application of evolutionary economics appreciates the demand-driven element of innovation but emphasises technological input as the main limiting factor; as argued by Nelson: “differences in “effective demand” account for only a small portion of the uneven evolution of know-how that we have experienced” (Nelson, 2008:487). This is based on the importance of practice and learning in knowledge accumulation (Nelson and Winter, 1982, Nelson, 2003, 2008). In this, the knowledge underlying innovation is integral to standardising and understanding the outcome of experiments (ibid). Therefore, the distance between scientific knowledge and its application is a key factor in influencing the rate and direction of innovation (Nelson, 2003, 2008, 2011), which in turn influences the ability to appropriate benefits from investment in R&D (Klevorick et al., 1995). One area of research has focused on this role of experimentation as an important factor in innovation and, in particular, the importance of animal models in predicting the behaviour of a technology when applied to the human body (Nightingale, 2000, Yaqub, 2008, Nightingale and Yaqub in press).

The ‘systems of innovation’ framework, another application of evolutionary economics, highlights the institutions and organisations involved in innovation and the interactions between them (Nelson, 2011). ‘Systems of innovation’ have been applied on various levels; national systems (Freeman, 1995), sectoral systems (Malerba, 2002), and technological systems (Chang and Chen, 2004). Studies implementing the systems framework to identify the drivers of medical innovation emphasise: the importance of the scientific base and the institutions supporting it, intellectual property and healthcare-science interfaces (Metcalfe et al., 2005); and, specific to the case of rare diseases: orphan drug policies, knowledge sharing and the benefits to the organisation’s image (Moors and Faber, 2007).

These applications also highlight the importance of the role of coordination in terms of communication of research outputs both between organisations (Powell, 1996) and between research groups working on parallel experiments within organisations (Nightingale, 2000). Evidence shows that this kind of coordination of R&D processes directly influences the success of technological projects (Ramlogan et al., 2007).
The sociology of science and technology literature provides both an insight into the factors influencing innovation, and a number of issues that allow for an appreciation of a more complex picture. In this nuanced view, sociology emphasises the embedded nature of scientific and technological knowledge, providing a critique of the evolutionary perspective in light of its reductionist approach (Sarewitz, 1996).

From a sociological perspective coordination is an integral facilitator in the communication of scientific findings. This coordination is necessary for the creation of shared visions of the future possibilities of a project, thereby allowing for the production and projection of expectations. In this innovation can be perceived in terms of the crucial role of promises, visions and expectations which facilitate its progression; necessary due to the uncertainty surrounding the nature of a market that is yet to exist (Borup et al., 2006). These expectations further influence decision making processes in organisations by facilitating the mobilisation of resources and managing uncertainty in disciplinary fields, in addition to feeding back into coordinating research efforts (Guice, 1999, Sung and Hopkins, 2006). Furthermore, expectations are integral to building and supporting rhetorical claims, and constructing realities (van Lente and Rip, 1998). The complex dynamics of stakeholder interaction in medical innovation, and the inherent difficulty of forecasting market demand further highlight the important role played by expectations and feedback mechanisms (Gelijns and Rosenberg, 1994).

The framing of research projects, and their subsequent success, is also influenced by social movements. For instance, Epstein describes and analyses the role of the homosexual community in the rapid development of anti-retrovirals to treat AIDS/HIV (Epstein, 1995). This literature emphasises the influence of public groups on technological advancement and innovation (Brown and Zavestoski, 2004). Despite this relatively established area of literature, there is also an argument that emphasises a different direction of causality, where pharmaceutical companies influence patients, who in turn, influence policy (Abraham, 2010). This is also the case in the influence of the media on public opinion, where both positive and negative impacts result from the amplification of successes and failures of research projects (ibid). It is clear that innovation is driven by social influences such as the media, patient groups and the strategies for communicating science and technology, employed by stakeholders. These rely on the influence of ‘framing’ on the perception of opportunities and decision making processes.

This thesis is by no means the first attempt at integrating economic and sociological perspectives in analysing medical innovation. Significantly, a contribution by Blume outlines
an analogous approach by identifying the macro level processes involved in the development of medical technologies (1992). Blume uses the ‘career’ of a technology as a powerful conceptual tool to consider the context of the different stages through the progression of innovation (Hopkins, 2004, Hopkins, 2006). This historical approach represents a holistic view of the socio-economic environment and the influence of stakeholders, contributing towards each stage of development (Blume, 1992). Therefore in addition to identifying factors contributing towards innovative success, it is also necessary to appreciate the longitudinal and contextual narratives surrounding these processes.

In summary, this review of the theoretical literature has taken into account a diverse set of conditions contributing towards the progress of innovation, using a multidisciplinary framework. These are, from an evolutionary economics perspective: 1) scientific and technological knowledge base; 2) demand of the market; and 3) system of innovation; and from the STS perspective: 1) the construction of expectations of the project, which feeds into 2) the influence of public perception, the media and policy makers. These conditions formulate the theoretical framework which will facilitate categorising the more operationalised factors that are identified from the empirical literature (table 1). In addition, this theoretical literature review has highlighted the importance of a contextual approach to understanding the processes contributing to successful drug innovation, an input most salient in the upcoming discussion of methodology choice.

**Empirical literature**

To enhance the theoretical discussion it is helpful to look beyond the aforementioned fields and to the wealth of studies that analyse rare diseases, spanning health economics, medical and ethics journals. In this extensive empirical literature review articles mentioning ‘rare diseases’ or ‘orphan drugs’ have been categorised into 7 themes: 1) evaluation, review and analysis of the ODA, 2) factors influencing innovation, 3) ethical discussions, 4) case study analyses, 5) the construction/classification of the term ‘rare disease’, 6) the influence of patient advocacy, and 7) general industry/strategy analysis.

In this review the largest group of papers (39 of 122 articles) are concerned with the ODA, of which there are roughly equal numbers critiquing versus complementing it. There are 3 major critiques of the ODA: 1) high prices commanded by orphan-designated drugs (Arno et al., 1995, Hughes et al., 2005, Dear et al., 2006, Simon, 2006, Enzmann and Luetz, 2008, Hemphill, 2010, McCabe et al., 2010, Wellman-Labadie and Zhou, 2010, Simoens, 2011); 2) safety of such drugs due to the low numbers used in clinical trials (Kesselheim et al., 2011, Kesselheim, 2011, Dupont and Van Wilder, 2011); and 3) broad interpretation of ‘orphan’
instigating the designation of drugs for non-rare indications (Yin, 2009). This lack of agreement surrounding the ability of the ODA to stimulate the production of new drugs for rare diseases indicates signs that additional strategies are required. This provides justification for the aim of this research – to provide potential additions to policy aimed at encouraging innovation of drugs for rare cancers.

Table 1: Summary of the factors influencing drug innovation for rare diseases as identified from the empirical literature review, grouped into categories identified from the theoretical literature.

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Opportunity, Market size, Prevalence, Purchasing power, Return on investment, Chronic/Acute (Simmons, 2003, Jha et al., 2010, Webber and Kremer, 2001, Projan, 2003, Orofino et al., 2010, Heemstra et al., 2009, Pablos-Mendez et al., 1999, Fehr et al., 2011, Trouiller et al., 2001)</td>
</tr>
<tr>
<td>Social Framing</td>
<td>Patient groups, Expectations, Promotion, Adoption (Pablos-Mendez et al., 1999, Boon and Moors, 2008)</td>
</tr>
</tbody>
</table>

In the literature discussing the factors influencing drug innovation, there are studies of the barriers to drug innovation both in the industry in general (DiMasi, 1995, DiMasi, 2001), and in the case of rare diseases. The factors discussed in these papers can be grouped into the broad areas defined in the theoretical literature review (summarised in Table 1). Despite this exhaustive list, it is difficult to identify policy recommendations from these studies due to the lack of information regarding the interactions between the factors and the nature of the causal relationships. This motivates an additional aim of the research – to identify relationships between the causal factors influencing drug innovation for rare diseases. This aim draws on the complexity of the factors determining success (or failure) as has been illustrated in detailed case studies of the drug innovation process (see e.g. Bazell, 1998).
LITERATURE GAP
From the theoretical literature it is clear that multiple factors contribute towards a complex system of interrelated actors and interactions to influence drug innovation and its distribution amongst different diseases. However, a study to identify the factors, causality and interactions between them has yet to be carried out. In addition to the need for a detailed analysis of drug innovation for rare diseases, it is also apparent that in medical innovation there has been a lack of studies which produce conclusions that can be applied more broadly, due to the small samples usually implemented. It is the combination of these two disparities that provide the contribution of this research.

RESEARCH QUESTIONS
The main aim of this research is to identify the conditions influencing medical innovation and the interactions between them, across a number of cases. This will enable conclusions to be drawn with reference to a holistic picture of the system allowing for policy recommendations to be made. The following research questions will demonstrate how these aims will be satisfied:

1) What conditions of rare cancers contribute towards their successful treatment with therapeutics?
2) Assuming a complex web of interactions exists, what combinations of these causal conditions determine successful treatment of rare cancers?

RESEARCH DESIGN
In order to address the research questions a Qualitative Comparative Analysis (QCA) will be implemented. A QCA aims to explain an outcome in line with the conditions that contribute towards that outcome. This method satisfies the literature gap by providing a balance between qualitative research methods, focusing on in-depth analysis of a particular case, and quantitative research methods, which broaden the scope of a research project in analysing multiple cases (Ragin, 1987, 1994, 2000).

The reasons for not using a regression model (which would also lead to understanding an outcome in terms of its explanatory factors) are; firstly, a regression analysis, unlike a QCA, tends to treat explanatory factors as causally independent, where factors influence the outcome regardless of the action of others, and the overall influence is taken to be additive. Secondly, a regression is limited to quantitative data. Finally, regression models take factors to be permanently causal, as opposed to QCA, which allows for asymmetry. Causal asymmetry implies that both the presence and absence of the same condition may lead to the outcome in different combinations of conditions.
Despite originating in political sciences, QCA has more recently been applied to a wider disciplinary arena (see [www.Compasss.org](http://www.Compasss.org)) (Berg-Schlosser et al., 2009, Yamasaki and Rihoux, 2009). QCA utilises set theory and Boolean algebra to analyse cases according to configurations of characteristics (conditions) that define them (Rihoux and Ragin, 2009). The use of set theory allows for the categorisation of cases in line with their set relations, or relationships between conditions (or combinations of conditions) (Ragin, 2008:2). Set relations are particularly suited to studying social phenomena due to their proximity to the natural language often used in hypothetical propositions (ibid). This proximity, between QCA as a method and the conceptual framing used in social sciences, also supports its use in problem-oriented research.

The logic of set theory is operationalised in QCA by employing Boolean algebra to deal with set membership and set relations. Broadly speaking this involves classifying conditions as true (present) or false (absent) and then comparing cases using logical operators. These operators include: ‘intersection’/multiplication (logical AND), ‘union’/addition (logical OR) and ‘negation’ (logical NOT) (Smithson and Verkuilen, 2006:4-6). The major benefit of Boolean algebra is its combinatorial logic allowing for a holistic picture of the empirical situation, where cases are defined in the way they relate to each other through causal intersection (Ragin, 1987:13-15).

When QCA was first suggested as a method for analysing social phenomena it relied on a dichotomised coding system (crisp set analysis) which limited the level of set membership to either full membership (1), or full non-membership (0). Although this simplified and increased the speed of analysis it did not facilitate a nuanced view of the cases. In response to this a new ‘fuzzy logic’ was applied to QCA (Zadeh, 1965). One example of the difficulty in categorising cases using a dichotomous system is the case of ‘y’ and its membership into the sets ‘vowels’ or ‘consonants’, where ‘y’ is sometimes used as a vowel but is usually categorised as a consonant. This suggests that there is no characterisation which would accurately represent its membership into one or the other (Smithson and Verkuilen, 2006). Fuzzy logic provides a solution by allowing categorisations to be represented in terms of partial membership, thereby facilitating a more fine grained distinction between cases. In the social sciences, fuzzy set theory allows for the translation of natural language into membership scores, providing a pathway to incorporate qualitative and quantitative approaches (Smithson and Verkuilen, 2006:38, Ragin, 2008).

Despite the relative straightforward technique of QCA it relies on foundations that facilitate high quality analyses. The main points for consideration are: 1) the choice of the conditions
to be measured and how they might be operationalised, 2) the calibration of the conditions, a process which requires knowledge of external standards which contribute towards the classification of cases as full, or partial, members/non-members of a condition/set, and 3) select the relevant cases within which the research is most relevant.

As discussed in the previous section, the strategy for choosing the conditions to be measured in this analysis was guided by an assessment of the theoretical literature in the first instance, with further detail informed by the empirical literature.

Building on the choice of conditions, it is then necessary to translate the collected raw data into fuzzy set scores, called calibration. Calibration relies on theoretical and substantive knowledge of the cases, empirical context and conditions. This is a conscious and purposeful process that moves away from the allocation of relative measures, such as averages or standard deviations, present in quantitative research. The allocation of scores in calibration is based on concept formation relating to what is meant for a case to be categorised as having full membership into a particular set, and the interpretation of this within the context of the scholarly community.

There are three ways of assigning fuzzy set scores, depending on the type of data used and the concept being represented. One commonality between these approaches is the central role of qualitative anchor points providing a point of reference at which cases are fully in, fully out and neither in nor out (Schneider and Wagemann, 2012:30-35, Ragin, 2000:170). These points carry qualitative and empirical meaning throughout the analysis and provide a focus for calibration.

The first approach, and that which is implemented in the present study, is the ‘theory-guided strategy’. This involves manually assigning fuzzy set scores to the raw data for each case. This strategy is particularly suited to conditions incorporating qualitative and quantitative data. The other two strategies involve the utilisation of computer software to assign fuzzy set scores. These will not be discussed further in this paper (however, see Schneider and Wagemann, 2012:33-35 for a detailed discussion). Due to the iterative nature of the method and the strong link between calibration and concept formation, it is common for calibration to be re-visited multiple times during the analysis.

When the calibration is complete the next step in the analysis is the construction of a truth table. This allows for a presentation of the data facilitating the configurational design of a QCA. A truth table is characterised by the transferral of data from a matrix into a format where rows represent all possible combinations of conditions (e.g. table 2). This allows the
researcher to decipher relationships between conditions, in line with the empirically observed cases. In particular, truth tables facilitate the identification of sufficient conditions.

In a truth table the outcome condition is usually coded as Y. The level of membership of a case to a condition is coded in terms of 1 and 0 (or in fuzzy set analysis, such as this, as its proximity to 1 or 0). ‘1’ represents full membership or presence of a condition, ‘0’ represents full membership or absence of a condition.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>Y (outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2: hypothetical illustration of the relationship between a truth table and the solution output of a QCA (AB + Ac -> Y)

The output of a typical QCA is a solution made up of the conditions (or combinations of conditions) which are found to be sufficient. This solution is then translated into a proposition about the cases, and the relationship between the causal conditions and their outcome, in terms of sufficiency (predominantly) and (sometimes) necessity. For instance, from table 2 the solution would initially be (taking all the rows that contribute towards the presence of the outcome): ABC + Abc + Abc -> Y (where upper case letters indicate where the condition is present, and lower case letters where the condition is absent). This could then be minimised to AB + Ac -> Y because the C in ABC is seen to be irrelevant because both ABC and Abc are accounted for through the sufficiency of AB. Similarly, Abc and Abc are both accounted for through Ac. This final solution (AB + Ac -> Y) can be interpreted to mean that both the presence of A and the presence of B are sufficient for Y to occur, or the presence of A in combination with the absence of c are sufficient for Y to occur.

**DATA AND RESULTS**

In the present application of QCA the unit of analysis is types of cancers. These were defined from the Pharmaprojects database to overcome the issue of the various
classifications of cancers by different organisations. In total a group of 12 rare cancers were identified: Mesothelioma, Chronic Myelogenous Leukaemia, Ewing Sarcoma, Chronic Lymphocytic Leukaemia, Neuroblastoma, Small Cell Lung Cancer, Acute Lymphocytic Leukaemia, Hodgkin’s Lymphoma, Acute Myelogenous Leukaemia, Kaposi Sarcoma, Osteosarcoma, and Gastrointestinal Stromal Tumours.

The outcome to be measured was defined as ‘well treated with chemotherapy’. This was determined in line with the aim of the study and the aforementioned research questions. The conditions are (identified from the theoretical literature review): 1) high market demand, 2) extensive and applicable scientific and technological knowledge, 3) thorough system of innovation, and 4) supportive social framing.


The operationalisation of the conditions, and they way they are subdivided into measurable factors, depends on the unit of analysis. In the present study the type of cancer represents the unit of analysis. With reference to table 1 (summarising the factors from the empirical literature review) the following factors were found to be relevant to this study (also see fig. 1):

1) Well treated with chemotherapy:
   a. Targeted or cytotoxic treatments (i.e. affecting the growth of cells in general or specifically targeting cancer cells)
   b. Typical/overall survival of patients
   c. Role of chemotherapy in treatment regimens

2) High market demand
   a. Overall prevalence/incidence
   b. Typical age at onset
   c. An idea of the typical price historically obtained for chemotherapy agents

3) Extensive and applicable scientific and technological knowledge:
   a. Number of academic publications mentioning the cancer
4) Thorough system of innovation
   a. The state of diagnosis of the cancer and whether there were national screening programmes
   b. Number of research groups quoted to be registered in Europe and aimed at research relating to the cancer
   c. Number of expert centres, again registered in Europe and aimed at research relating to the cancer

5) Supportive social framing:
   a. Number of newspaper articles mentioning the cancer
   b. Number of patient organisations supporting that cancer

As QCA is a case-oriented method the process of calibration began with brief case studies of each cancer. Due to space restrictions not all case studies could be included in this paper; however one (for CLL) is included as an appendix (appendix 1). The resulting calibrated conditions are presented in table 3.
The calibrated data was then input into QCA software for analysis, in this case fsQCA\(^3\) was used. In the first instance a truth table output is generated (see table 4). To aid the analysis of this truth table consistency values are calculated to indicate the level of sufficiency of each combination of conditions. Consistency values represent the extent to which a condition (or combination of conditions) is sufficient, representing a measure that indicates the how well the data are represented in the resulting conditions. In other words “set theoretic consistency assesses the degree to which the cases sharing a give condition or combination of conditions agree in displaying the outcome in question” (Ragin, 2006).

Table 4 shows that the highest values of consistency are shown for 2 combinations: 1) the presence of ‘high market demand’ (M) AND ‘extensive and applicable scientific and technological knowledge’ (K) AND ‘thorough system of innovation’ (S) AND ‘supportive social framing’ (F) (MKSF) (0.86) and 2) for the presence of ‘high market demand’ (M) AND ‘extensive and applicable scientific and technological knowledge’ (K) AND ‘thorough system of innovation’ (S) AND the absence of ‘supportive social framing’ (MKSf) (0.88). It is these two rows that are deemed to be sufficient for the outcome to occur, given their high consistency values.

\(^3\) Free software downloaded from [http://www.u.arizona.edu/~cragin/fsQCA/software.shtml](http://www.u.arizona.edu/~cragin/fsQCA/software.shtml) (1/8/12)
Table 4: QCA truth table output

<table>
<thead>
<tr>
<th>Market (M)</th>
<th>Knowledge (K)</th>
<th>System (S)</th>
<th>Social (F)</th>
<th>number</th>
<th>Outcome (Y)</th>
<th>raw consist.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.96</td>
<td></td>
</tr>
</tbody>
</table>

A simple process of logical minimisation indicates that the social framing (F) condition is irrelevant, where the outcome is clearly associated with the influence of the presence of ‘high market demand’ (M) and ‘extensive and applicable scientific and technological knowledge’ (K) and ‘thorough system of innovation (S) (MKS), whether or not ‘supportive social framing’ is present. Therefore the simplest output from this analysis is MKS -> Y. This indicates that in order for the outcome to occur, i.e. for a cancer to be well treated with chemotherapy, high market demand, extensive and applicable scientific and technological knowledge, and a thorough system of innovation, should all also be present. In other words, the conditions, high market demand, extensive and applicable scientific and technological knowledge and a thorough system of innovation are sufficient (in combination with each other) for the outcome to occur.

This is confirmed by looking at the conditions contributing towards the absence of the outcome (i.e. the absence of a cancer being well treated with chemotherapy). The solution for this scenario is mks + kSf + mKsf -> y. This indicates that either the presence of the system condition (in the absence of the knowledge condition and the absence of social framing), or the presence of knowledge (in the absence of all remaining factors), or the absence of all factors, all contribute to the absence of the outcome condition.
An alternative analysis also confirms a similar solution. This alternative analysis differs only in the process of calibrating the macro conditions (e.g. high market demand) using the measured factors (e.g. prevalence/incidence). In this process, rather than the calibrations being done manually with consideration of how one factor might interact with another, as implemented previously, the calibration was completed with the logic of the AND or OR operators from Boolean algebra. In this approach the first decision is to conclude from theoretical and substantive knowledge, for each macro-condition, whether there is a need for all of the factors to be present (i.e. AND) or whether only one of the factors present could contribute towards the macro-condition (i.e. OR). Once this is decided logic tells us that, in the case of an AND relationship it is necessary to take the minimum fuzzy set score as a representation of the overall score. In the case of an OR relationship it is necessary to take the maximum fuzzy set score as a representation of the overall score. The reason for this is that in an AND solution, the overall score is only as strong as its weakest component.

In this analysis it was concluded that in order to be well treated with chemotherapy products a cancer must have targeted therapies, high survival rates and chemotherapy must play an important role (therefore the AND operator was used and the minimum fuzzy set scores taken). For high market demand it was suspected that either having high prevalence, relatively young age at onset or history of having gained a high price would be sufficient (therefore the OR operator was used and the maximum fuzzy set scores taken). For both extensive and applicable scientific and technological knowledge (where the number of publications, their discipline and the number of clinical trial studies were important) and thorough system of innovation (where ease of diagnosis, many research groups and expert centres were playing a role) the AND operator was used. And finally, for supportive social framing it was concluded that either having high visibility in newspaper articles, or many patient organisations supporting the cancer would be enough to indicate a supportive social framing (therefore the OR operator was used).

When this analysis was carried out the resulting solution was found to be: MKSf -> Y (i.e. the presence ‘high market demand’ AND extensive and ‘applicable scientific and technological knowledge’ AND ‘thorough system of innovation’ AND the absence of ‘supportive social framing’ were sufficient for the outcome to occur). This partially supports the previous solution where the common factors are the presence of high market demand, extensive and applicable scientific and technological knowledge and thorough system of innovation, however, the role of the social framing remains in contestation between the two solutions.
A possible resolution to this problem can be addressed by assessing the differences between the solutions in terms of the values for consistency and coverage. The consistency values (where consistency indicates the extent to which the solution is sufficient for explaining the outcome) for the two solutions are 0.829787 (for MKS -> Y i.e. the first analysis solution) and 1 (for the MKSf -> Y i.e. the second analysis solution). In addition coverage values present another parameter for making sense of the significance of the solutions by indicating the extent to which all of the empirical observations are explained by the output solution. For the two solutions the coverage values were as follows: MKS -> Y = 0.7222 and MKSf -> Y = 0.26087. These indicate that the first solution (MKS -> Y) explains a higher proportion of the cases than the second (MKSf -> Y) and, as both have relatively high consistency values, it can be concluded that this higher coverage value contributes towards a more accurate solution.

There is one main limitation to this study: the issue of limited diversity. Limited diversity is thought of as a problem of studying social phenomena and the limited amount of variation that exists in social reality (Ragin, 2000). This implies that in a QCA, where all possible combinations of conditions are considered, it is common for a large number of counterfactuals to appear i.e. combinations of conditions that are not empirically observed. A strategy to attempt to minimise, or at least not predetermine the existence of counterfactuals, is to ensure that the number of cases is greater than the number of possible combinations of conditions (as calculated by $2^n$, where n is the number of conditions). In this study, 12 cases were studied, and categorised in line with 4 conditions (16 possible combinations). In this case it is clear that at least 4 of the possible combinations will not be observed because there are not enough cases to satisfy this. This problem can usually be overcome by adding more cases however in this study the subsample of rare cancers (taken from Pharmaprojects) was too small. An alternative strategy would be to reduce the number of conditions measured, however again in this case, this would be problematic.

**DISCUSSION**

These results indicate one main conclusion: that the presence of a combination of three conditions are sufficient for the outcome (i.e. for a cancer to be well treated with chemotherapy products) to occur. These conditions are high market demand, extensive and applicable scientific and technological knowledge, and thorough system of innovation.

The inclusion of these conditions was informed by the theoretical literature review. High market demand was inferred to be important from initial discussions of its role as a main driver of innovation in the 1960s. The condition for scientific and technological knowledge
was developed in line with both the ‘science push’ model and the application of the evolutionary economics approach that suggests an importance of the applicability of scientific research and the distance between science and practice in driving innovation. The condition for the system of innovation also came from an application of the evolutionary economics perspective which emphasises the role of different institutions that support innovation and the interaction between these institutions.

In response to the potential for this conclusion to be thought of as mundane and/or uninformative it is interesting to highlight that these conditions are not sufficient to cause the outcome on their own. For instance, high market demand is not, independently, a sufficient condition for the successful treatment of a particular cancer. This is in direct contestation to the premise that market demand is the only driving force motivating drug innovation. Similarly, the other conditions do not show a direct and independent sufficient relationship with the outcome and are equally reliant on the presence of the other two conditions for the outcome to occur (confirmed when the presence of single conditions, in the absence of others, is found to contribute towards the absence of the outcome). This is a significant finding because it lends itself to a shift towards a need for a plural perception of the process in question and the environmental conditions which need to be present in order for drug innovations to be successfully developed. It is this aspect which is not being accurately portrayed in the policies aimed at addressing the issue of rare diseases, and therefore those under which personalised medicine will be addressed in the future.

The notion that policies are thought of in either ‘push’ or ‘pull’ terms, highlights the simplistic perception of the process at hand. Furthermore, this highlights the inability for policies aimed at either push (generally associated with the science push model) or pull (generally associated with market pull) factors to influence innovation for rare disease drug innovation. For instance increasing funding for research into rare diseases or the introduction of advanced market commitments (where private firms are incentivised by the predetermined guarantee that a number of their approved drugs will be sold to organisation such as WHO) would, under the conclusion of this study, be ineffective. This brings to light a unique opportunity for the drug innovation process, and the policies used to address issues associated with this process, to be viewed of in terms of a set of interconnecting and dependent conditions which act together to produce the outcome, in addressing clinical need.

It is this conclusion that would not have been facilitated if a regression analysis was implemented. This is mainly due to the inability for a regression model to infer causal
interactions, where these methods tend to be limited to net effects and causal independence. Furthermore, it would have been impossible, in the implementation of a regression analysis, to draw conclusions from the subsample of rare cancers (and thereby draw conclusions based on diseases that affect small populations) due to the small number of cases.

Despite this insight into the process of drug innovation and the potential for this conclusion to feed into informing policy, there is a necessity for further research. One avenue for this is to refine the measures contributing towards the calibration of the macro-conditions. The predominant reason for this is the discrepancy in the two output solutions found in the different types of calibration and the suggestion that the non-inclusion of social framing in any scenario might be a conclusion that may need to be refined in line with common sense observations. Furthermore the contribution from the theoretical literature which has outlined the potential for social framing to have both negative and positive effects, something that would not be captured in the calibration process so far.

In addition it is expected that further research will be carried out to assess drug projects (again bounded by those aimed at rare cancers) that have shown varying degrees of success. One of the potential limitations of this type of analysis is in the difficulty of categorising drug projects in terms of success and how success might be defined conceptually. An alternative to this might be to extend the current analysis to a large population of types of cancers, to include those that are more common and therefore extend the conclusions to the population of cancers as a whole, as opposed to the subsample rare cancers analysed in this study.
BIBLIOGRAPHY


DOLGIN, E. 2010. Big pharma moves from 'blockbusters' to 'niche busters'. Nature Medicine, 16, 837.


MAZZUCATO, M. & DOSI, G. 2006. The evolution of pharmaceutical innovation


WELLMAN-LABADIE, O. & ZHOU, Y. 2010. The US Orphan Drug Act: Rare disease research stimulator or commercial opportunity? Health Policy, 95, 216-228.


Web 4: http://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/default.htm
APPENDIX 1: Chronic Lymphocytic Leukaemia

Synonyms: Chronic Lymphoid Leuk(a)emia, lymphoplasmacytic leuk(a)emia, small lymphocytic leuk(a)emia. Subtypes include: B Cell CLL, Prolymphocytic leuk(a)emia, Large granular lymphocyte leuk(a)emia, hairy cell leuk(a)emia.

General Information:

CLL is the most common subtype of leukaemia. Under the umbrella of CLL are other forms of leukaemia, where B-cell CLL is the most frequent. Although there is no standardised staging system for the disease, the two most commonly used are the Rai (characterised by Stages, 0, I, II, III, IV) and the Binet (clinical stages A, B and C). There are several genes mentioned to be associated with CLL: ARL-11, ATM, CCND1, IGHG1, IGHV and TP53, however, the genetic basis of CLL remains poorly understood.

Well treated with chemotherapy:

As a chronic form of leukaemia, CLL is generally associated with slow progression and has even been the subject of over-diagnosis, where a patient is diagnosed by chance and in cases where the disease may not have had a detrimental impact on their life otherwise. There are several types of treatments, associated with different stages of disease. These include watchful waiting, radiation, chemotherapy, combination therapy, and stem cell transplantation. Watchful waiting is usually implemented in stage 0, with the introduction of chemotherapy, low dose radiation and stem cell transplantation in stages I, II, III and IV. In refractory stage patients are advised to consider entering into clinical trials. Prognosis is generally dependent on the stage at which the disease is identified and can range from a few months to normal life expectancy. Generally patients in stage 0 are expected to survive 12 years, stages I and II – 7 years and stages III and IV – less than 1 year. The chemotherapy agents approved for use in patients with CLL are rituxumab (rituxan) (targeted mAb – approved 1997), alemtuzumab (Campath) (targeted mAb - approved 2001), chlorambucil (ambochlorin, Leukeran, Linfolizin) (cytotoxic - approved 1957), ofatumumab (Arzerra) (targeted mAb - approved 2009), bendamustine (Treanda) (cytotoxic - approved 2008), cyclophosphamide (Cytoxan, Neosar) (cytotoxic - approved 1959) and fludarabine phosphate (fludara) (cytotoxic - approved 1991). These therapeutics provide a good balance between targeted and cytotoxic therapies, however the standard recommended treatment in the UK is rituximab in combination with fludarabine and cyclophosphamide, hence combining older cytotoxic agents with more modern targeted mAbs.

Fuzzy set score for ‘well treated with chemotherapy’: 0.8 (more in than out)

Justification:

- High survival rates, and long term prognoses
- However, with slow progression it is perceived that this survival rate is less dependent on chemotherapy agents
- Large number of targeted agents

---

4 All approval dates in this section refer to FDA approval.
**High market demand:**

Occurrence of CLL is stated to be 5.8 per 100,000 in men and 3 per 100,000 in women in the USA. Despite the slight disagreement in figures (between the NCI and NICE, who state that the incidence is 2.7 people per 100,000 in the western world) it is commonly perceived as the most common form of leukaemia worldwide. Mortality rates are 2.1 per 100,000 in men and 0.9 per 100,000 in women in the USA. The cost in the UK of one of the chemotherapy agents, rituximab, is estimated at £10,128 per course, lasting a total of 24 weeks, with the highest Incremental Cost-Effectiveness Ratio (ICER) reported to be £22,661 per QALY gained (well below the threshold imposed by NICE of £30,000 per QALY). Onset of CLL is usually over the age of 60 years (in 75% of cases), with only 6% of cases occurring below the age of 50.

Fuzzy set score for high market demand: **0.6** (more in than out)

**Justification:**

- Old age at onset, therefore treatment period is short
- No history of first line treatment exceeding the NICE threshold
- Low incidence rates but the most common form of leukaemia

**Extensive and Applicable Scientific and Technological Knowledge:**

Up to the present day (with analysis carried out in November 2012) there had been 21,704 publications mentioning CLL. These began in 1949, although before 1960 there were only 19 papers published mentioning the cancer. Subsequent to this the frequency of CLL publications increased gradually, until the 1990s when they quadrupled (from 1,514 to 4,839), and again in 2000s (from 4,839 to 10,330), with half of all publications mentioning CLL appearing in the 2000s (10,330 of the 21,704 total). These trends are illustrated in the figure below.

![Frequency of CLL publications, categorised by discipline type](image)

5 Although the actual numbers are different owing to the duplications created by the dual categorisation of publications by WoS into more than one discipline.
Furthermore it is clear that, although there is an increasing trend towards publications in the basic sciences the majority of publications are located in the applied sciences, with a very small proportion categorised as social sciences. In terms of the output of translated research into clinical research in the form of clinical trial studies, there are 1,244 clinical trial studies for CLL, B-cell CLL or Hairy cell CLL (the three major forms of CLL), excluding duplicate records. This is a substantial number of clinical trials studies.

Fuzzy set score for extensive and applicable scientific and technological knowledge: 1 (fully in)

Justification:
- High amount of knowledge produced in the form of publications mentioning CLL
- High proportion of applied knowledge
- High level of translation of research into clinical trial studies
- However, remains uncertainty over the genetic causes of the disease

**Thorough System of Innovation:**

There are 150 expert centres for CLL, 89 diagnostic test centres, 32 research projects, 29 registries/biobanks and 20 networks. Overall this seems to represent a substantial amount of interest in the disease from the system as a whole. Furthermore, according to one CLL support organisation there are 27 CLL specialists in the UK alone.

Fuzzy set score for thorough system of innovation: 0.8 (more in than out, almost fully in)

Justification:
- Large numbers of organisations and networks aimed at supporting the system surrounding CLL

**Supportive social framing:**

As with other types of leukaemia, the social framing of CLL is influenced by the broader perception of it as a disease, and being the most common CLL would be expected to receive a large proportion of this interest. This is illustrated in the number of patient organisations aimed at leukaemia and lymphoma (16 in Europe). Furthermore, there are other groups for both CLL and leukaemia in general across the English-speaking world = CLL Support Association, Leukemia and Lymphoma Society, Leukemia Research Fund, CLL Information Group, CLL Research Discussion Group, CLL Canada and the CLL Forum. In addition CLL in its own right shows a moderate level of interest from the media (in the form of mentions in newspaper articles), where a total of 3,505 articles were found, with a sharp increase seen from 1990s (178 articles) to 2000s (2,218 articles = on average one every two days). This is likely to represent a lagged result of the increasing knowledge coming out of the scientific knowledge base, as noted above.

Fuzzy set score for supportive social framing: 0.4 (more out than in)

Justification:
- Popular culture support of leukaemia in general
- Moderate number of newspaper articles mentioning CLL (3,505)
- Large number of patient organisations (23) in support of leukaemia and lymphoma in general, although, again the extent to which this influences CLL in particular is in question