The role of patents in the development and clinical use of genetic tests

FINAL REPORT (Deliverable 3b)

Case studies on the role of IP in the development and clinical use of genetic tests for Factor V Leiden, TPMT and HPV in the USA and EU

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The ETEPS AISBL – European techno-economic policy support network has been set up on the initiative of the Institute for Prospective Technological Studies (IPTS) of the European Commission. Its main mission is to provide intellectual services for carrying out techno-economic and policy-related studies in the context of EU policy-making.

The ETEPS network is organised as a legal entity – the ETEPS AISBL, founded in 2005 by 19 effective members from 15 EU Member States. It further counts 19 associated members worldwide and is supported by a network of external organisations.

The main activities of ETEPS are:

- Undertaking scientific research on the interdependencies between science, technology, economy and society, with a focus on foresight and evaluation;
- Developing and using scientific models, data and other related tools to improve the scientific understanding of European Science & Technology related policies; and
- Taking appropriate actions to disseminate the knowledge thus gained.

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Executive Summary

The project "Intellectual Property and Diagnostics" has been commissioned by the European Commission through the Institute for Prospective Technological Studies (IPTS). The project investigated the current implications of molecular diagnostic patents for the development and clinical use of pharmacogenetic testing. There has been considerable concern about the possible negative impact of patenting and licensing practices on diagnostic research and testing carried out by clinical laboratories and the possibility that patent thickets may hamper development of new tests by manufacturers. Ranged against this is the increasing importance of biomarker IP to many companies in the IVD sector, in particular companies developing molecular diagnostics.

The analysis provides information on:

1) Companies involved in developing relevant diagnostic tests, and their experiences of exploiting their patents as well as the challenges posed by the patents of other organisations in the development of their products and services.
2) The extent to which European clinical diagnostic laboratories are able to develop and offer molecular diagnostic tests in the current environment.
3) The experiences of patient organisations with respect to accessibility of genetic testing and the assumed impact of patents.

This part of the analysis, entitled " Case studies on the role of IP in the development and clinical use of genetic tests for Factor V Leiden, TPMT and HPV in the USA and EU" is based on interviews with together with analysis of publicly available information from the websites of stakeholders, published biomedical literature, patents, and legal documents. These case studies can provide key lessons for future licensing, diagnostic service provision, and the development of policy in this field.

A prominent feature of all three cases has been the exclusive licensing of biomarker IP by public sector organisations to small or medium-sized firms. Our three case studies illustrate three completely different approaches to exploiting such IP:

- FVL – owner and exclusive licensee do not develop a test kit, but license the patent to others who do so
- TMPT - company in-licenses suite of IP to develop Laboratory Developed Tests (LDT) in the its own reference laboratory with the aim of creating a monopoly on patient access to the test (TPMT);
- HPV - company develops a test kit which is sold to multiple laboratories but prevents other kit manufacturers from entering the market.

The findings reinforce some key findings from WP2

- a definite trend towards companies holding intellectual property in biomarkers. This is true across the industry, encompassing large and small, new and old firms, and companies producing test kits and those providing tests from their own reference laboratories;
- a lack of certainty about the true value of biomarker IP and the best way to exploit its commercial and clinical potential;
- European molecular laboratories have experienced less negative effects from patenting than US laboratories, enforcement against labs is still relatively uncommon;

- little evidence of access problems for patients.

The case studies are important because they allow us to test some of the generalisations of WP2 by examining in detail the complex ways in which biomarker IP interacts with other factors to affect the R&D process, clinical uptake and patient access to new tests. Key findings include:

- Patents on genes are just one form of IP relevant to genetic testing, and these case studies have shown that there may be significant limitations restricting how companies can exploit this IP, indicating that the biological context of the patented invention as well as the specific claims the patent holder has been awarded substantially influence a patent's likely commercial impact.

- All three cases involve patent holders in the private sector and the public sector and in each case much of the key IP has come from the public sector. This indicates that the issues arising from the acquisition and exploitation of biomarker IP are not attributable simply to the pursuit of competitive advantage between biotech firms. The case of FVL illustrates that the nature of the contract between licensor and licensee may have a substantial impact on subsequent enforcement activity.

- Patents in genetic testing have not consistently provided monopolies for IP holders. In all three cases laboratories are infringing patents, and often are doing so without any apparent threat of enforcement by the IP holder. The case which most resembles BRCA is TPMT were the company has commercialised the test as a Laboratory Developed Test (LDT) in its own reference lab and has actively enforced its IP to prevent other US labs from performing the test. However, the long-term success of this strategy remains to be seen, since there are two separate law suits which are yet to be settled. Digene have pursued a similar strategy of enforcing their IP through litigation in the US but not in Europe. Again they have met with mixed success, although thus far they have a virtual monopoly on the US market.

- There are significant differences in company strategies and outcomes in the US and Europe in the case of HPV and TPMT, although less so for FVL. The range of laboratories and kit manufacturers producing rival tests is far greater in Europe than it is in the US. These regional differences mirror the BRCA case and provide further support for a trend we identified in WP2.

- The impact of biomarker IP on the development and diffusion of the tests varied widely between cases. In the case of FVL the patent holder has a longstanding involvement in clinical studies to further elucidate the clinical significance and utility of the test and to identify new markers. The HPV case is also one where the chief patent holder has made a major commercial investment in clinical studies. TPMT is the case where there seems the weakest link between biomarker IP and investment in clinical studies, although it must be borne mind that in the cases of both HPV and FVL there has been significant public investment in clinical studies as well.

- In the case of both HPV and TPMT there seems to be a strong correlation between market exclusivity and a willingness to invest significant sums in sales and marketing. Prometheus and Digene/Qiagen have each used their own sales force to target doctors to generate demand for the test. In the case of Digene this is an unusual departure, since kit manufacturers do not generally promote direct to physicians, preferring instead to target laboratories who will then in turn promote the test to doctors. Digene have gone even

further in their pursuit of market growth by engaging in direct-to-consumer promotion, in a clear parallel with Myriad's promotion of the BRCA test.

A new basis for progress in the field?

This report illustrates the strength of the case study method for hypothesis falsification. On this basis three widely-held views about gene patents can be put aside as having been negated or requiring significant qualification:

1. *Are gene patents uniquely problematic in terms of being difficult to invent around*? In fact they are not infallible, may be invented around, and other forms of IP can also be disruptive in this field.

2. *Is exclusive licensing always problematic in genetic diagnostics?* It may be, in some cases, but more could be done in the drafting of exclusive licensee agreements to include terms which might prevent some problems from emerging.

3. *Are patents on genes are sufficient incentive on their own to ensure large-scale private investment to validate tests?* They may do in some cases, but there are clearly limits to the investment firms make when faced with diverse requirements of national markets and difficulties in promoting their products across these markets; the scale of investment may be linked to the potential size of the market and likely return on investment and publicly funded research continues to play a major role in validation of tests.

The case studies presented here demonstrate that while the BRCA case offered policymakers an early indication of some of the issues that may arise from the growing importance of biomarker IP in the molecular diagnostics sector, a single case can at best provide only a partial understanding of the range of strategies for exploiting such IP and the variety of potential outcomes. It is hoped that these additional case studies create a fuller picture. Generalisation from these cases should be undertaken with care as it must be borne in mind that the sector is moving very rapidly and some of the greatest challenges in dealing with biomarker patent thickets (which clearly is what the HPV case may be called) may arise in applications not covered in these cases. As noted in our WP2 report, an increasing number of companies are developing polygenic tests for applications such as measuring heritable susceptibility to common diseases or molecular profiling of tumours for prognosis and treatment selection in post-operative cancer patients. Such applications have considerable potential for problems arising from royalty stacking and may make the need to develop coherent policies to manage the challenges of biomarker IP more pressing. Given the heterogeneity of approaches and experiences we have revealed it is unlikely that there is a single set of solutions to the issues raised by the trend towards biomarker IP. Policymakers who wish to support innovation in the molecular diagnostics sector whilst ensuring patient access to valuable new tests will have to adopt different strategies in different circumstances. In doing so they must accept that they are operating in uncertain and rapidly shifting terrain.

I. Introduction

1.1 Background to the study

Intellectual property rights (IPR) have been generally considered an important incentive for innovation as they facilitate the sharing of new knowledge (from inventions) with the scientific community and society as a whole, while guaranteeing that a part of the totality of financial rewards that may accrue from the innovation will be provided to the patent holder. Patents reward the inventor with the exclusive right to exploit the invention but only when accompanied by full disclosure of the invention, and for a limited time. This is usually up to 20 years following the date the patent application was filed with full disclosure, and is considered sufficient time to recoup the investment made for the invention. Applications of modern biotechnology, such as recombinant therapeutic proteins and vaccines (e.g. Erythropoietin and Hepatitis B vaccine), are being increasingly patented. The birth of high-throughput genomics and proteomics has facilitated this trend further allowing a greater numbers of, and increasingly refined, studies of gene function and disease susceptibility.

In spite of its stimulating effect on innovation, intellectual property has also been suggested to potentially inhibit research as a result of the proliferation of DNA patents[1], resulting in limited access to novel treatments and diagnostics (e.g. as a result of high licensing fees.[2] This argument is particularly supported by cases where patent holders made broad claims or exerted strict monopoly rights (e.g. Myriad Genetics holds or has licensed several patents on the breast cancer genes BRCA1 and BRCA2 and exerts strictly its monopoly rights in the USA by not allowing testing of the genes outside its laboratory).[3] Further evidence in this direction is provided through a recent study indicating the negative impact of patenting and licensing practices on diagnostic research and testing carried out by clinical laboratories.[4]

Although some reports have argued that substantial empirical evidence to support the potentially inhibitory effects of IPR on research is still lacking,[5] a wider concern with regards to diagnostic tests remains, especially as emerging techniques allow the detection of multiple mutations at a time (microarray-based tests) to diagnose disease susceptibility or drug disposition (National Research Council 2005). In this context, the development of patent thickets (a situation where different owners have overlapping patent rights requiring multiple licences) could pose a significant barrier. The emergence of new uses for pharmacogenomics in research and development, as well as in the clinic, may further complicate the situation.[6]

[1] Jensen, K and Murray, F (2005) Intellectual property landscape of the human genome. *Science* 310: 239-240.
[2] Cho, M.K et al (2003). Effects of patents and licenses on the provision of clinical genetic testing services. *Journal of Molecular Diagnostics* 5: 3-8.
[3] Matthijs, G (2004). Patenting genes. *BMJ* 329: 1358-1360; Parthasarathy, S (2007) *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics in Health Care* MIT Press
[4] Cho, M.K et al (2003). Effects of patents and licenses on the provision of clinical genetic testing services. *Journal of Molecular Diagnostics* 5: 3-8.
[5] Verbeure, B; Matthijs, G and van Overwalle, G (2006) Analysing DNA patents in relation with diagnostic genetic testing. *European Journal of Human Genetics* 14: 26-33
[6] Barton, JH (2006) Emerging patent issues in genomic diagnostics. *Nature Biotechnology* 24: 939-941.

Pharmacogenomics[7] refers to the application of genomic tools (e.g. the identification of single-nucleotide polymorphisms, the development of refined sequencing techniques, microarrays and computational tools) to the study of multiple genes with the aim of elucidating disease mechanisms, understanding better drug response and adverse drug reactions (ADRs), but also of facilitating drug development.[8]

Recent evidence indicates that intellectual property rights may present a significant barrier to pharmacogenomics research and the development of related tests.[9] The type of patents that may be issued to protect such tests would likely cover combinations of biomarkers associated with other features e.g. drug efficacy or response. A proliferation of such patents could create major difficulties for further development of diagnostics if the patented sequences are associated with multiple phenotypes. In this case it would be required that several licences are acquired prior to developing a particular test, with potentially serious cost implications.

One additional consequence of pharmacogenomics is the disruption of the blockbuster model and limitation of drug markets to a significantly smaller size (in terms of sales), as a result of identifying non-responders. According to some,[10] the potential loss of sales revenue is a major disincentive for drug companies which may use patent rights to steer away the application of pharmacogenomics in development. Yet, pharmacogenomics also offers the potential to minimise the cost of clinical trials by identifying patients who might experience ADRs at an earlier stage. In this case large pharmaceutical companies may choose to pursue the development of relevant diagnostic tests themselves or turn to the expertise of smaller diagnostic companies. Patents would play a key role in such interactions.

Surprisingly though, a recent IPTS study mapping patenting activity shows that only half of the core companies involved in pharmacogenetic test development actually held patents explicitly focused on pharmacogenetic applications (although it is not known what the situation is like regarding applications as the field is relatively young).[11] Similarly the actual impact of related patenting and licensing practices on the diagnostics industry and the associated consequences on healthcare are not well documented. The present study sets out to clarify some of these uncertainties, including the impact in molecular testing of intellectual property, effect of patents/licences on performing and developing molecular diagnostics, dynamics in patenting and information requirements and ethical concerns about patenting/licensing of molecular diagnostics.

A specific problem that is addressed in this project deals with the access to genetic tests. The patenting of genes or parts of them is discussed already since the Human genome project started. Ethicists and others state that genes are not an invention per se. They argue that because genes are part of 'mother nature' they belong to all and should not be exploited by pharmaceutical companies who sell the genetic diagnostic tests.[12] Some authors even argue that patents on genetic testing could be harmful for society.[13]

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[7] It stems from the field of pharmacogenetics which involves the study of genetic variation on inter-individual differences in drug response with the aim of tailoring therapy accordingly.

[8] Zika, E; Gurwitz, D; and Ibarreta D (2006) Pharmacogenetics and pharmacogenomics: state-of-the-art and potential socio-economic impact in the EU. European Commission DG JRC/IPTS, EUR 22214.

[9] Zika, E; Gurwitz, D and Ibarreta D (2006) Pharmacogenetics and pharmacogenomics: state-of-the-art and potential socio-economic impact in the EU. European Commission DG JRC/IPTS, EUR 22214.; Nuffield Council (2003) Pharmacogenetics: ethical issues. Report. Nuffield Council on Bioethics, London.

[10] Eisenberg, RS (2002) Will pharmacogenomics alter the role of patents in drug development? *Pharmacogenomics* 3: 571-574.

[11] Zika, E; Gurwitz, D and Ibarreta D (2006) Pharmacogenetics and pharmacogenomics: state-of-the-art and potential socio-economic impact in the EU. European Commission DG JRC/IPTS, EUR 22214.

[12] see for instance: Merz, J and Cho, M (1998) Disease genes are not patentable: a rebuttal of McGee. *Camb Q Healthc Ethics*. 7(4):425-8

[13] Norrgard, K (2008) Diagnostic Testing and the Ethics of Patenting DNA *Nature Education* 1(1)

There has been concern that patented genetic tests will create access problems for patients in the EU (Matthijs, 2006).[14] This study aims not only to investigate whether such access problems exist but also what role (positive or negative) patents play in the development and use of molecular genetic diagnostic tests.

The analysis provides information on:

1) Companies involved in developing relevant diagnostic tests, and their experiences of exploiting their patents as well as the challenges posed by the patents of other organisations in the development of their products and services.
2) The extent to which European clinical diagnostic laboratories are able to develop and offer molecular diagnostic tests in the current environment.
3) The experiences of patient organisations with respect to accessibility of genetic testing and the assumed impact of patents.

Other outputs from this project have been a global survey of the molecular diagnostics industry to identify key company data such as size, age, products / services, R&D activity, and collaborations with private and public partners (WP1), a series of 17 interviews with selected companies in Europe and North America, a survey of European genetics labs (and a series of follow-up interviews) and interviews with patients organisations in Europe (WP2).

1.2 Methodology

Three case studies have been undertaken to reveal the context of the development and clinical use of patented genetic tests. A case study approach was adopted in part as a response to the fact that a great deal of the policy discussion on gene patents and genetic testing has hitherto focused on a single case: Myriad Genetics and the BRCA patents. Whilst other evidence has been brought to bear, such as the laboratory survey conducted by Cho et al, the major focus on this single case was suggestive of the need for more in-depth comparative analysis of multiple cases (a similar approach has recently been adopted in the USA on behalf of the SACGHS Task Force and the cases we have selected are complementary to this ongoing US research the findings of which are yet to be published). The chief methodological benefit of the case study approach is that allows the research to go beyond simply identifying trends to seek detailed answers concerning how and why something is happening. It affords the opportunity to generate and test hypotheses.

A comparative study of the US and three European countries also allows the opportunity to assess whether national differences in the organization of biomedical research and delivery of healthcare, play a role in how biomarker IP is exploited and in the development and diffusion of molecular diagnostics. The initial focus of the study was on three classes of diagnostic tests, as set out in Table 1. Case selection took place through a two step process. Firstly, high profile examples of tests with substantial potential use were listed, including examples where patent disputes had been largely avoided (e.g. Cystic Fibrosis). Initial literature and patent searches on these genetic tests were presented at a team workshop (in June 2008). This discussion formed the second stage of the selection process where the novelty of each case (i.e. not duplicating existing work by other groups) was held to be paramount. Cases were to be chosen from across the categories of Table 1, including tests that could be called pharmacogenetic as well as those that are not pharmacogenetic and to provide some opportunity to demonstrate contrast between regions (e.g. in the presence and absence of key patents in the regions studies) and did not proceed with computations. Selected cases are emphasised in bold in Table 1.

[14] Matthijs, G (2006) The European opposition against the BRCA gene patents. *Fam Cancer* 5(1):95-102

Table 1. List of potential case studies considered

Area	Initial case studies	Main reasons selected/ not selected
Mendelian Traits	Cystic Fibrosis	Reported elsewhere
	HFE-Associated Hereditary Haemochromatosis	Reported elsewhere
	Factor V Leiden Thrombophilia	**Widely used – not studied in detail elsewhere**
Disease Stratification	Breast Cancer (gene expression profiling)	The BRCA test is well covered – too close to this.
	Lung Cancer(gene expression profiling)	Insufficiently established test usage
	Human Papilloma Virus	**Patented but possibly not well exploited – does strong patent position have an influence?**
Drug Metabolism	**Thiopurine Methyltransferase**	**Widely used test - contrasting US/ EU patent situation**
	Cytochrome P450 Oxidoreductase Deficiency	Insufficiently established test usage

After the case selection process more detailed patent searches were undertaken on the three selected cases using commercial databases.

Cases were selected on the basis of patents being in force, in the EU or USA, on genes or parts thereof, on methods or kits. The case studies are based on publicly available information from the websites of stakeholders, published biomedical literature, patents, and legal documents. Where possible, interviews with relevant stakeholder groups have also been undertaken. Four groups of interviewees are especially relevant and have been the focus of empirical research: (i) Holders of key patents or licences covering the genetic test in question (ii) Clinicians using the test (iii) licensees of the patent, whether service providers or kit developers and (iv) non-licensees of the patent, whether service providers or kit developers. The interviewees are referred to (e.g. in Table A) by their role (i.e. clinical laboratory, kit maker) rather than whether they are a licensee or non-licensee. For the TPMT case study Prometheus were interviewed but we were unable to use the material from them due to regulatory compliance issues.

This project has focused on the development and clinical use of tests in Germany, the Netherlands, the UK and USA. Up to four interviews have been undertaken in each country studied per case, with the aim of covering a range of stakeholder views to provide an **exploratory view** and summary of the salient features of the case study as required for a high-level comparative analysis. The cases provide an overview of a range of relevant issues. They cannot be used to assess the prominence of the views expressed or the extent to which these are typical or atypical of the wider stakeholder groups interviewed.

Interviewees have been asked to contribute their experiences and views anonymously, although since it is obvious from the details of the cases which institutions are the key patent holders, where these institutions and their exclusive licensees are interviewed responses are not entirely anonymous. In areas where details anonymity is possible, the case study does not reveal the interviewee's nationality (where possible) and with finalisation of the analysis, transcripts/ recordings/ draft cases will be destroyed to further ensure the protection of anonymity. These are deemed necessary steps to promote disclosures and ensure as full an exploration of the issues as possible, for the benefit of societies seeking to optimise their science and technology policies. **In all cases the views expressed are those of the interviewees and these views are not necessarily shared by their employer.**

Table 2: Participants for interviews

	Key holders of relevant intellectual property	Testing labs (excluding key IP holder)	Kit makers	Clinicians
FVL	1 university (EU) 1 kit maker	5 EU labs, 2 US	2 EU, 1 US	4 EU, no US.
TPMT	1 US university 1 US testing laboratory	6 EU, 1 US	3 EU 1 US	3 EU 1 US
HPV	I kit maker	3 EU, 2 US	1 EU, 1US	3 EU

Case studies are structured around the following questions:

1. What is the biological basis for the test?
2. What is the patent position and how have assignees exploited this?
3. What tests are available and how are they used?
4. What is the clinical utility and cost-effectiveness of the tests?
5. What lessons can we learn from this case about patenting & the development and use of diagnostics

II. Factor V Leiden

2.1 Introduction

Factor V Leiden is a mutation in a gene associated with increased risk of thrombosis. Key patents are held by a European university and were exclusively licensed to a European diagnostics company, who make sub-licenses available to kit manufactures. Whilst a number of test kits are available, many laboratories continue to test using their own LDTs, often infringing the patent. Factor V Leiden has become one of, if not *the*, most common genetic tests for heritable markers in both Europe and the US. Its uptake in clinical practice was rapid and it is noteworthy for being used by haematologists and family doctors rather than clinical geneticists. Despite well-established and longstanding clinical use of the test, there is still lack of conclusive evidence on its clinical utility and controversy surrounding its apparent over-use.

2.2 Biological background [15]

Management by the body of the formation, dissolution, and re-absorption of blood clots is termed haemostasis. It is mediated by proteins responsible for coagulation and anti-coagulation. The Factor V and Factor II (FII) Prothrombin genes, amongst others, code for proteins that play a role in coagulation. Mutations in either of these genes may lead to an increased tendency to form blood clots, termed thrombophilia. Equally a number of genes code for proteins involved in anti-coagulation. Thus deficiencies of antithrombin, protein C or protein S are associated with thrombophilia. Other genes also play a role including Methylenetetrahydrofolate reductase gene – MTHFR, VWF gene, Factor VIII. [16] Inventors working in the field suggest that:

'Coagulation Factor V (FV) is one of several essential proteins of the coagulation cascade. In its activated form (FVa) it serves as a cofactor to activated factor X (FXa) in the activation of prothrombin to thrombin. FVa is inactivated by activated protein C (APC) which cleaves FVa at three sites'.[17]

The Leiden mutation is a single nucleotide change in the FV gene that causes the substitution of a single amino acid in the protein (arginine 506 is substituted by glutamine). This abolishes the primary APC cleavage site and gives rise to a pro-thrombotic state.[18] The Factor V Leiden mutation is just one of several known mutations that occur in the same gene. FVL may be inherited, and it is possible to be an autosomal heterozygote or homozygote.

Hereditary thrombophilia is a condition that leads to an increased tendency to develop blood clots within the blood circulatory system. Blood clots may form in any part of the body, but are particularly likely to form in large blood vessels found peripherally (legs and arms) and in major organs such as the heart, lungs and brain. Once a clot forms, emboli can separate from the main clot causing smaller clots in distant parts of the body. Clots are associated with swelling and pain.

[15] Unless indicated otherwise, the information in this section is derived from the medical information section of the UK patient support group 'Contact-a-family'. In that context, the information was approved in 2002 by Prof. F Cotter, Professor of Experimental Haematology, St Bartholomew's Hospital, London, UK. http://www.cafamily.org.uk/Direct/h41.html
[16] Patent application published in 1999 (GB2338062)
[17] Patent application published in 1999 (GB2338062)
[18] Patent application published in 1999 (GB2338062)

They deprive areas of the body of oxygenated blood leading to tissue damage. In the brain such clots cause strokes and have a high risk of causing long term disablity. Thrombosis and emboli can be life threatening. Therapies are available for dissolving existing clots and preventing formation of new clots (e.g. warfarin or heparin).

The discovery of the FVL mutation was published in Nature in 1994 by Bertina et al, working at the Rijks Universiteit in Leiden, in the Netherlands.[19] The mutation is found in approximately 3-5% of Caucasians, but 15%-20% of consecutive patients presenting with their first venous thrombosis.[20] It is more common than mutations in prothrombin and anticoagulant deficiencies. Except for the FVII 10976G/A polymorphism, FVL is associated with the highest hazard ratio of 15 'putative' genetic risk factors for thrombosis.[21]

2.3 FVL patents and key assignee exploitation strategies

The key patents associated with FVL relate to nucleotide sequences that can be used as probes to detect the FVL mutation, methods for detection and kits comprising genetic tests for the mutation. Phenotypic assays based on enzymes and anti-bodies have also been patented.

Both genotypic and phenotypic tests are used to confirm the status of patients thought to be at increased risk of thrombosis, either predicatively, or following a thrombotic event. Such testing might be used to inform patient management in a wide variety of situations (See section 2.4 for a discussion on the clinical utility of such interventions).

After Bertina and Reitsma's discovery of the FVL mutation, their employer, the Rijks Universiteit Leiden, filed for patents in early 1994, prior to the publication of their findings in Nature. The University's patents and key claims are summarized in Table 1. A number of other organisations have also filed patent applications or have been granted patents related to FVL (as set out in 2.3.2 and 2.3.3).Further details of these patents are set out in Appendix B. The exploitation strategies of the key assignee and their licensors are outlined (2.3.4). It is also noteworthy that assays based on activated protein C resistance (an important phenotypic test in thrombophilia) were also patented, but not by Leiden. A full investigation of patents covering the APC test was beyond the scope of this study, however it is clear that following the discovery of APC, just prior to the discovery of FVL, Swedish scientist Bjoern Dahlbaeck filed for patent on APR assays in Europe and the USA. These were granted (see EP0608235, and US5443960), despite number of diagnostics companies filed oppositions at the EPO, including bioMérieux (this was from 1996 onwards – prior to their own interests in FVL IP). By contrast, the opposition to the FVL patents was much less marked, involving only one company, though still a feature of the EPO process in this case.

Another interesting related finding is that the published claims for Leiden patents appear broad enough to cover certain phenotypic tests, for example claim 23 for the EP '325 patent claims the following:

'[A kit] comprislng one or more proteases capable of cleavage at the non-mutated APC cleavage site and Incapable of cleavage of the mutated APC cleavage site, or one or more proteases ca-

[19] Bertina, RM et al (1994) 'Mutation in blood coagulation factor V associated with resistance to activated protein C' *Nature* **369**:64.
[20] Rosendaal, FR et al (1995) High risk of thrombosis in patients homozygous for Factor V Leiden (Activated Protein C Resistance) *Blood* **85**: 1504-1508; Vandenbroucke, JP et al 'Factor V Leiden: Should we screen oral contraceptive users and pregnant women?' *British Medical Journal* **313** 2 November 1127-1129.; Baglin, T (2004) 'Management of Thrombophilia: who to screen?' *Pathology of Haemostasis and Thrombosis* **33** 401-404.
[21] van Hylckama, VA et al (2008) 'Proof of principle of potential clinical utility of multiple SNP analysis for prediction of recurrent venous thrombosis' *Journal of Thrombosis and Haemostasis* **6**:751-754.

pable of cleavage at the mutated APC cleavage site and Incapable of cleavage at the non-mutated APC cleavage site, an antibody capable of specifically recognizing a site on the aa 306-506 fragment of Factor V and/or Factor Va, an antibody capable of specifically recognizing a site on the aa 507 -679 fragment of Factor V and/or Factor Va'

However a well placed interviewee believed only antibody and genotypic tests were claimed by the Leiden patents. This highlights just how complicated patent claims may be to unpick.– although we know of no commercial dispute in this case.

Table 3: Rijks Universiteit Leiden's patent coverage relate to detection of a specific mutation

	USA	EU (DE, NL,UK)
Genotypic	Probes and Method ('016)	Probes that hybridise to the mutation site, methods and kits ('325, '691)
Phenotypic	Enzyme (APC) or antibody ('256) Anticoagulant response ('913)	Methods and kits using Enzyme (APC) or antibodies ('325)

2.3.1 Assignees and key claims for granted patents

In 1998 a university in The Netherlands, the Rijks Universiteit Leiden was granted EPO patent No. 696,325 on a method for screening for the presence of a genetic defect associated with thrombosis and poor anticoagulant response to activated protein C. In 2001, Rijks Universiteit Leiden was granted a further EPO patent on a FVL diagnostic test. Together these patents cover a broad range of methods and kits for detection of the FVL mutation, including nucleic acid analysis, antibody detection of the mutated protein and tests based on cleavage of Factor V and Va by activated protein C (although one interviewee disputed the coverage of the latter – as noted in previous section). The Rijks Universiteit Leiden patent estate also includes patents claiming the key nucleotide sequences in relation to FVL. Following this Rijks Universiteit Leiden was granted a series of US patents including a method for diagnosing an increased risk for thrombosis or a genetic defect causing thrombosis and kit for use with the same that shows their continued interest in patenting mutations related to thrombosis, such as in the Prothrombin gene. In 2001, Rijks Universiteit Leiden was granted another EPO patent on a FVL diagnostic test. In 2003, Rijks Universiteit Leiden was granted a further two US patents on FVL diagnostic tests. Although three US patents have been granted they cover similar claims to the EPs. Thus, the Rijks Universiteit Leiden appears (interviewee counter-claims notwithstanding) to have patents relevant to both phenotypic and genotypic tests based on a range of methods as well as patents on the gene mutation itself, in both the US and Europe. The Rijks Universiteit Leiden patent estate includes patents claiming the key nucleotide sequences in relation to FVL, but not the whole gene.

Another assignee is Promega (a US company) granted a US patent on a specific mutation detection method for the FVL mutation, in 2001 (now expired) and 2003 (in force). Thirdly, Vermont University was also granted a US patent on a mutation detection method in 2001 but it expired due to failure to pay the maintenance fee. Fourthly, Mayo Foundation (a US medical education and research hospital) was granted a US patent on a simplified mutation detection method and nucleotide primers in 2002. Mayo Foundation also filed a PCT application, which appears to have

been abandoned. Fifthly, Douglas Thien, one of the inventors of patents related to FVL diagnostic test, owns three US patents on nucleic acid sequence detection employing probes comprising non-nucleosidic coumarin derivatives as polynucleotide-cross linking agents originally granted to Naxcor (a US company) in 2001, 2002 and 2004 (now expired). Sixthly, Cleveland State University was granted a US patent on a method for genotyping single nucleotide polymorphisms related to FVL in 2002. Finally, Ravgen (a US company) was granted a US patent related to FVL diagnostic method test in 2007. Further details of these patents can be found in appendix B.

2.3.2 Other applicants

Apart from the assignees of granted patents, twelve relevant patent families contain applications filed either at the USPTO, EPO or WIPO by a variety of applicants, including companies, academic institutions, public agencies and individuals. These patent applications mainly protect methods. However, five of these patent families contain applications that have been abandoned/ withdrawn in both the USA and EU and another two are abandoned in the US. Dhallan Ravinder, Ravgen, TM Biosciences US DHHS and University of Florida all appear to have pending patent applications at the EPO. Further details of these applications can be found in appendix B.

2.3.3 Exploitation strategies

The Rijks Universiteit Leiden chose to exclusively license their FVL patents to a local company, Organon Technica. While the exact date was not available, Organon Technica's molecular diagnostics business was subsequently been taken over by bioMérieux in 2001, who are now the exclusive licensee and responsible for granting sub-licences. An interviewee at Rijks Universiteit Leiden viewed the licensing collaboration had been successful. Objectively it does appear that the test is widely used and the exclusive licensee has granted a number of sub-licenses, in contrast to some other prominent cases of exclusive licensing associated with DNA patents.

In particular Organon Technica had been helpful in the prosecution of the patent and had paid for the costs of the application. A US kit manufacturer suggested that this sort of exclusive licensing deal suited universities because it would yield a high upfront payment for the technology transfer office and relieve them of the task of dealing with multiple non-exclusive licensees. FVL was viewed as having been well validated by studies at Leiden and elsewhere (US kit maker). Thus an EU kit manufacture suggested that bioMérieux had been making money for doing very little.

A US kit maker reported that bioMérieux were asking a high single digit royalty from kit makers (e.g. less than $1.15 per unit on a kit with a sale price of $11.50 per unit for laboratory users, based on the prices charged for a leading provider). An EU kit maker confirmed a high single digit royalty rate would meet their expectation for this kind of test. The labs that use commercial kits show client list prices of $150 or more, although the actual reimbursement price is often lower, perhaps $90, the US kit maker suggested. Indeed one US lab suggested reimbursement could be $50-60. The US kit maker thought there might be an incentive to purchase kits sold with a license rather than to take out a sub-licence directly to offer a service as the same royalty rate applied to the service provider may cost them $9-$15 in royalties. The Rijks Universiteit Leiden itself was not involved in the negotiation of sublicences, but they suggested at interview that the royalty negotiations might be based on the effort to develop the invention, the number of potentially interested licensees and the importance of the invention, while for the licensee the number of patients and market size were primary considerations.

It is not clear how many sub-licenses exist but it is public knowledge that bioMérieux have granted sub-licences to the patents for FVL and their commercial position is clearly enhanced as they hold rights to mutations in the FII (prothrombin) gene also patented by Leiden. The two risk

factors are often used together in kits and laboratory services. Non-exclusive licences for both sets of IP were granted to kit makers Tm Bioscience and Gen-Probe in 2003 and 2004 respectively. Test users would also have to pay for a licence for PCR reagents, according to the US kit maker. However some labs are now using platforms with tests for FVL working independently of PCR (US lab).

In 2003 Roche became the first company to obtain FDA approval for a kit that detects FVL as well as mutations in the gene for FII. The kit is now one of several CE marked and FDA approved products on the market for FVL detection. Roche's kit, for use on their Light Cycler™ platform, was initially launched as a kit for research use only in 1999/2000 but this has subsequently obtained FDA approval for use as an IVD. It is not clear if Roche had a sub-licence for FVL and FII (the product information leaflet contains no mention of a licence, and is not required to do so). However two industry interviewees (an EU kit maker and US kit maker) emphasised there was a commercial imperative to take a patent licence when filing for FDA approval on their products. In part this imperative is due to the financial investment (suggested as perhaps $2m-3m for a genetic test such as FVL) required to obtain FDA approval as this would be wasted if the patent owner or licensee were able to obtain an injunction against the sale of infringing kits.

The Rijks Universiteit Leiden continues to publish studies on clinical utility of the test, and indeed is doing so with at least one kit manufacturer (Celera) who is combining the FVL test with other loci. [22] However a kit maker suggested there is little commercial incentive to invest in research on FVL if any resulting growth in utility and market size cannot be appropriated by that investor.

2.3.3.1 Enforcement

Kit makers in the EU and US suggest there has been little if any enforcement of the patents, with one kit maker questioning the value of paying the licence fee. Several kit makers were suspected of selling kits without licences and most labs in the US and EU were thought to offer the test without a licence, according to kit makers (discussed further in section 2.4). The interviewee at Rijks Universiteit Leiden indicated patent enforcement is the duty of bioMérieux but that Leiden had asked that the patent is not enforced against individual academic research institutions. The exclusive-licensee, bioMérieux, was not available to comment on this.

The US kit maker interviewed suggested it was counter-productive for companies selling diagnostic tests to sue their customers for patent infringement. However they suggested failure to litigate might also indicate weaknesses in the underlying IP, or that the costs of litigation were likely to exceed the damages awarded. Of course this would not stop patent owners or their licensees from sending 'cease and desist' letters and threatening to sue. It does seem that this had been done in at least one case as FVL is mentioned in a list of tests at least one laboratory in the US had had to withdraw due to patent enforcement activity[23] but it does not appear that a FVL testing service has been the subject of litigation to date.[24]

[22] van Hylckama, VA et al (2008) 'Proof of principle of potential clinical utility of multiple SNP analysis for prediction of recurrent venous thrombosis' *Journal of Thrombosis and Haemostasis* **6**:751-754.
[23] Cho, M et al (2003) Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services *Journal of Molecular Diagnostics* 5(1): 3-8
[24] Holman, CM (2007) The impact of human gene patents on innovation and access: A survey of human gene patent litigation *University of Missouri–Kansas City Law Review* 76(295); http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1090562.

2.4 FVL test availability and usage

The discovery of Activated Protein C resistance (APC and APCr) in 1993[25] and publication of the Factor V Leiden mutation in 1994 by researchers at the Rijks Universiteit led to a rapid rise in thrombophilia testing.[26] This occurred even before the patent was granted. Rapid uptake in usage is ascribed to the ease with which the test could be used as well as because it was the first common genetic risk factor in its field (according to interviewed EU and US laboratories and a US kit maker). An interviewee from an EU lab noted "[FVL testing] was introduced very rapidly because of its importance…it was the first real kind of thrombotic risk factor…it was a significant advancement in the field".

At least ten commercial molecular genetic kits have been launched in the US and European market as a result of the large international market for FVL testing, although some appear to be used little (US lab, UK NEQAS survey data 2007). Indeed many (perhaps most) laboratories use homebrews (EU labs 1&2, EU kit makers 1&2). Even laboratories that have used commercial kits may convert to homebrews (EU lab, US lab). The marginal cost to laboratories of kits (as opposed to the fixed cost of staff) was expressed as one reason for this but in part this was suggested to be because laboratories were not able to find kits that had the functionality they required (EU lab). One US lab reported switching from an FDA approved kit to their own in-house test because it allowed them a substantial saving in costs. The suggested scale of savings (at least a halving of the reagent cost from over $25 per test to roughly $10) was confirmed by another US lab.

It should be noted that the phenotypic APC test, patented but not the prime focus of this case, has also been heavily commercialised. The FDA has approved APC tests from eight different manufacturers, all of which are class II IVDs that required pre-market notification prior to market launch. Up to the start of 2008, a further five kits have been approved for FV Leiden testing using molecular genetic techniques.

Laboratories in both the EU and US used a phenotypic test of thrombophilia (the APC resistance test) and genetic tests (often for panels of risk factors including FVL and FII), although practice clearly varies from lab to lab. For example interviewees in the UK and The Netherlands reported that tests are offered mainly by haematology laboratories rather than specialist clinical genetics laboratories, who are not equipped to undertake the APCR assays. Equally some haematology labs in The Netherlands and UK did report sending their samples away for genetic tests.

Laboratories reported that the APC test will detect a wider range of clotting problems but can give false positives while FVL is more precise and can detect the difference between patients that are heterozygous or homozygous for a mutation. US and EU labs reported that using the APC as a screen prior to then using genetic tests to identify specific anomalies is a cost-effective strategy (US lab, EUlabsx2). Although this is logical, as we will see in 2.4.2 this is not always used.

Amongst EU laboratories there was disagreement over the relative cost of phenotypic versus genotypic testing strategies, perhaps reflecting differences in methods or scale of operations, but Phenotypic and genotypic tests are used along side each other (EU labs x3, EU kit maker) the latter providing the definitive answer to the question 'does the patient have FVL?' as the phenotypic test is less precise and can yield false positives (EU lab). A molecular test can also distin-

[25] Dahlback B; Carlsson M and Svensson PJ (1993) Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: prediction of a cofactor to activated protein C. *Proc Natl Acad Sci LI S A*. 90:1004-1008.
[26] Baglin, T (2004) 'Management of Thrombophilia: who to screen?' *Pathology of Haemostasis and Thrombosis* 33: 401-404.

guish between FV Hong-Kong, FVL, and FV Cambridge (EU lab). In the UK the clinicians have discretion which tests they require, however one lab and a clinician reported that in practice clinicians simply 'tick the box' for a genotype test as well as the phenotypic test even though as the lab suggests this is sub-optimal:

"If your talking purely from a financial point of view, the most financially beneficial…would be to do an APCR first and anyone that has an abnormal…then go on and do the genotyping" (EU lab).

In the USA, Both CAP and ACMG state that the first-generation APC resistance assay had deficiencies in both sensitivity and specificity but that the second-generation test has specificity close to that of the DNA test and is cheaper. For most cases both guidelines state that either the second generation functional assay or the DNA test can be used but that if a functional assay is used that positive results should be followed up with a DNA test as a confirmatory test and to establish whether the patient is heterozygous or homozygous. CAP suggest that the DNA test should be the initial testing method for patients with a lupus anticoagulant and a markedly prolonged baseline activated partial thromboplastin time (aPTT) (which may interfere with the functional APC resistance assay) and for family members of subjects with known FVL mutations in order to avoid the need for follow-up confirmatory direct mutation testing.

2.4.1. FVL test availability and usage in the USA

2.4.1.1 Extent of testing

Laboratories reported using FVL from the mid-to-late 1990s onwards and by 2003 FVL was one of the most commonly performed genetic tests in the USA.[27] At present at least 70 labs (ranging from university labs to large private pathology laboratories) offer FVL services according to genetests.org, despite the suggestion by Cho et al. (2003) that at least one laboratory had withdrawn a service due to patent enforcement. While this number is a useful gauge of activity it is unlikely to be comprehensive.

2.4.1.2 Use of commercial kits/ licenses

As noted in section 2.3.3.1 and 2.4 above, a number of commercial kits are available for APC and FVL tests. However commercial tests for FVL are seen as expensive relative to the cost of basic reagents that laboratories can configure into (unlicensed and non-FDA approved) tests themselves with significant cost savings. In part this is driven by a desire by clinical laboratories to be price competitive with other providers. These pressures are not confined to the US healthcare system and are further discussed in the EU context below (in 2.4.2.2).

2.4.2. FVL test availability and usage in the EU

2.4.2.1 Extent of testing

[27] Hellmann EA, Leslie ND and Moll S (2003) Knowledge and educational needs of individuals with the factor V Leiden mutation. *J. Thromb Haemost* 1: 2335-9.

Thrombophilia testing predates current phenotypic and genotypic methods, with low levels of testing in specialist centres in the UK at least as early as the mid-1980s.[28] However the discovery of APC resistance and the Factor V Leiden mutation, in 1993 and 1994 respectively, led to testing growing exponentially in the 1990s. Baglin, a highly cited UK clinician suggests this rising volume of testing 'undoubtably arose as a response to association studies'. [29] Baglin's centre reported issuing 37 profiles in 1986, 600 profiles in 1993 and 3500 in 1999. [30] The FVL test has been used in the Netherlands since 1994, starting with just one laboratory offering tests for the whole country, but at least ten laboratories currently offer services following with rapid growth in FVL testing during the 1990s.

In the UK clinical laboratories adopted the FVL test following publication of research papers in the medico scientific literature from 1995 onwards (UK lab). Although the UK Government has recently sought to encourage the introduction of genetic testing services following the 2003 Department of Health White Paper[31] most of the investment in clinical services has been used to support specialist clinical genetics centres. However FVL and thrombophilia have long been diagnosed in laboratories focusing on Haemostatsis and thrombophilia and even general haematology laboratories (UK lab). These have remained outside the targeted government investment in genetics investment. A UK quality assurance scheme survey in 2007 attracted responses from 92 laboratories, although some of these will be from outside the UK.

Uptake of FVL testing in Germany also was rapid from the mid 1990s onwards. It has progressed to become a very widespread test (DE labs x2), and is one of, if not the most widely used genetic test in Germany according to interviewees. One kit maker claimed: "I know in Germany [FVL] is the second most run test after Fragile X" (EU kitmaker). A German lab contended that "it is surely the most tested molecular biology marker in human diagnosis" (DE Lab).

However, there are signs this may change. For example in The Netherlands it was noted that when FVL testing first emerged patients with thrombo-embolism were put on prolonged or even life-long anticoagulant treatment based on the presence of FVL, on the basis it was a risk factor for thrombosis and recurrence of thrombosis. However since then it has been suggested that risk of a second thrombosis is the same in FVL carriers and non-carriers, and as a result of this test use appears to be falling, from 2006 and perhaps earlier (NL clinician).

2.4.2.2 Use of commercial kits/ licenses

One EU kit maker lamented "I should think most labs are offering the Factor V as homebrew". However UKNEQAS survey data shows a wide variety of molecular genetic approaches are used for FVL testing, with several different commercial platforms being utilised (although this does not necessarily mean that laboratories are running commercial kits on these platforms, hence numbers are not reported here). Laboratories may choose to use in-house developed tests because commercial kits are a marginal cost for laboratories that has to be met in addition to fixed costs (staff). Interviewed labs supported their choice to use in-house tests as follows:

"the in-house test is cheaper, more robust, more reproducible, has built-in internal controls for contamination, distinguishes factor V Leiden mutation from other mutations at this position and

[28] Baglin, T (2004) 'Management of Thrombophilia: who to screen?' *Pathology of Haemostasis and Thrombosis* 33 401-404.
[29] Baglin, T (2004) 'Management of Thrombophilia: who to screen?' *Pathology of Haemostasis and Thrombosis* 33 p.402.
[30] Baglin, T (2004) 'Management of Thrombophilia: who to screen?' *Pathology of Haemostasis and Thrombosis* 33 p. 401.
[31] See Department of Health (2003) *Our Inheritance, Our Future – Realising the potential of genetics in the NHS*, Cm 5791. 24 June, The Stationery Office, Norwich. Available online at: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Genetics/GeneticsGeneralInformation/GeneticsGeneralArticle/fs/en?CONTENT_ID=4016430&chk=RnGBgL

the test can be multiplexed to obtain 3 genetic results [3 risk factors] in a single analysis. No existing kit offers this level of functionality" (EU lab1).

"I am adverse to commercial kits anyway and I suppose we had the assay up and running before any commercial [kits] came out…there's not been a driving factor to…convert to a commercial kit…we've got the equipment…which isn't being used to its full capacity.. its high throughput and not very labour intensive…it isn't the cheapest because [the reagents] are quite expensive but…the most expensive thing in laboratories is staff time."
(EU lab2)

Kit makers would argue that the higher price for commercial kits is justified:

"The benefits of having a commercial test now is that it will be CE marked and therefore…would have to have all the right things in place, technical files for review…the right level of quality control and quality assurance…vigilance procedures in place to report back any adverse events or malfunctions of tests or anomalous results none of which apply to in-house assays". (EU kit maker).

They continued:

"It's a benefit to the patient…whether you would consider it a benefit to the laboratory is questionable…laboratories are very resistant to changing over from their own homebrew to a commercial test that costs more…they do not seem to care whether a kit is marked for research use only, which has none of the back-up I mentioned…they're quite happy to use those that are very cheap to report clinical results on…..The scientist will say 'it's the same stuff in the box, it's just your paying extra for this extra you can't see. Is that fair?'" (EU kitmaker).

One EU lab suggested they saw a QC benefit to commercial kits but thinks that the advantage is less clear for larger well established providers than for small labs. Some labs have even tried to develop their own kits:

"A minority of laboratories may have embarked upon novel approaches and sought to patent successful ones, however patenting and commercialisation per se have not been a major driving force" (EU lab).

Indeed it appears that kit commercialisation in this market place is difficult. The interviewed lab that had tried to patent and commercialise a new method for testing had not had access to sufficient funds to gain wide patent coverage and had not found a commercial partner:

"The experience has been an extremely negative one. The lesson learnt is that patenting and commercialisation appear to be worth pursuing only if the product is likely to have a huge market, be highly marketable, and be of interest to major companies that have adequate resources for developing and marketing the product" (EU lab).

The laboratory also reported that they had not been able to obtain a licence for the PCR-reagents they had needed to support this test.

2.5 Clinical Utility and cost effectiveness

Thromophilia testing, including for FVL, is undertaken either as a screen for asymptomatic patients to plan preventative strategies or in patients who have had a thrombotic event to manage

the risk of recurrence. In both cases questions arise concerning the degree to which a positive result will change patient management in a way which can improve clinical outcomes.

2.5.1 Evidence for utility

Although numerous applications of the FVL have been suggested, clinical utility remains to be demonstrated. These are addressed in turn below.

Screening to predict pregnancy complications

Early calls for FVL screening of pregnant women and those requesting oral contraception have been resisted by those who discovered the mutation.[32] In 2002 a study of 957 pregnancies to assess the cost-effectiveness of universal and selective screening of pregnant women for FVL concluded that even when assuming highly effective interventions, a targeted screening program would not be cost-effective within the NHS.[33] Schleussner (2007) [34] suggests a more targeted approach, recommending testing in cases of thrombosis or related complications, of known incidences of thrombophilia in the family or following one late foetal loss or two early foetal losses from a patient. Yet subsequent research (2008) in a cohort of over 4000 pregnancies calls into question the role of FVL in pregnancy complications.[35]

Screening for recurrence of thrombosis

In a recent review article on thrombophilia, *CAP Today* reports that:

"Several studies support the notion that routine genetic testing or screening for thrombophilia is not beneficial. In one, deep venous thrombosis patients with a prothrombin mutation had a similar risk of venous thromboembolism recurrence at two and four years as those without a mutation."[36] The authors recommend that both patient groups require treatment of a similar duration. Another research team concluded that "[P]atients with factor V Leiden or the G20210A prothrombin polymorphism were not at substantially increased risk of recurrent events as compared to patients without these disorders. Moreover, the relative benefit of low-intensity warfarin therapy in preventing recurrent events was not significantly affected by the patient's genetic status".[37]

The article also report that two prospective studies of VTE/ DVT patients have found that testing for congenital thrombophilia did not predict recurrent venous thrombosis and that clinical factors are the best guide to treatment duration.[38] Baglin concluded "Now that high quality clinical outcome studies are being reported it is becoming apparent that despite association, testing [for heritable thrombophilic defects] has limited predictive value for the majority of unselected symptomatic patients. ... [I]n most cases decisions regarding intensity and duration of anticoagulant therapy can be made purely in relation to clinical criteria".[39]

However Baglin, working in the UK, leave some room for further debate in a series of papers (from 1998 onwards), suggesting that conclusive evidence, rather than the small patient number

[32] J.P. Vandenbroucke et al 'Factor V Leiden: Should we screen oral contraceptive users and pregnant women?' *British Medical Journal* 313 2 November: 1127-1129.
[33] Clark, P (2002) 'Cost-effectiveness of screening for Factor V Leiden mutation in pregnant women' *The Lancet* 359 1 June: 1919-1920.
[34] Schleussner E (2007) Thrombophilien als Schwangerschaftsrisiko. Empfehlungen zu Diagnostik and Therapie. *Gynaekologische Praxis.* 31(1): 41-52.
[35] P. Clark et al Greer (2008) 'The GOAL study: a prospective examination of the impact of factor V Leiden and ABO (H) blood groups on Haemorrhagic and thrombotic pregnancy outcomes' *British Journal of Haematology* 140 (2)pp. 236-240.
[36] De Stefano V, et al. *Brit J Haematol*. 2001; 113: 630– 635
[37] Ridker PM, et al. *New Engl J Med.* 2003; 348: 1425– 1434
[38] Baglin T, et al. *Lancet.* 2003; 362: 523– 526; Christiansen SC, et al. *JAMA.* 2005; 293: 2352– 2361
[39] *Pathophysiol Haemost Thromb.* 2003; 33: 401– 404

studies he reviews, are needed to demonstrate whether those with heritable thrombophilia are more likely to suffer an earlier recurrence of thrombosis, once treatment is stopped, than other patients.[40] This view was echoed by a senior representative of the UK's only patient group for thrombophilia at interview.

Baglin suggests the answer to this question may come from work being conducted at Leiden in the Multiple Environmental and Genetic risk Assessment of risk factors for venous thrombosis (MEGA) at the time of writing his 2007 paper.[41] Subsequently Baglin's Cambridge group and the Leiden group have reported on a large cohort study, in the UK and Netherlands, of 15 'putative' genetic risk factors for thrombosis including some in Factor V, Factor VII, Factor II, and MTHFR. This has shown that these genetic risk factors combine in only a small percentage of the populations in these countries (less than 4%). In individuals who have had a thrombosis and have two or more of the 15 SNPs (including FVL), risk of a recurrent thrombotic event is 50.3 per 1000 patient years while all remaining patients had a risk of 30.1 per 1000 patient years. This suggests that the clinical utility of SNP analysis is limited to only a small subset of patients.[42]

The website of the American Society of Hematology carries a number of pieces written by Dr Kenneth Bauer, Associate Professor at the Beth Israel Deaconess Medical Center at Harvard Medical School who states that:

"While we are able to identify laboratory abnormalities in a large percentage of venous thrombosis patients, this information cannot yet be used to target those requiring primary antithrombotic prophylaxis or most of those requiring extended secondary prophylaxis. The coming years will see progress in achieving these objectives as new hemostatic risk factors are identified and other laboratory tests (such as D-dimer) are incorporated into diagnostic algorithms derived from prospective studies. The present reality however is this: when a "hypercoagulable workup" uncovers abnormalities predisposing to venous thrombosis, the strongest risk factor for recurrence is the prior event itself, particularly if unprovoked or idiopathic."[43]

2.5.2 Guidelines for FVL use

Guidelines in the countries studied appear to reflect the evidence base, with an emphasis on the multi-factorial nature of thrombophilia and restraint in test usage, where mentioned.

The American College of Medical Genetics (ACMG) and the College of American Pathologists (CAP) both issued key guidelines in 2001.[44] Both CAP and ACMG state that it is not recommended for use as a general population screen, as an initial test in pregnancy or prior to or during oral contraceptive use, or hormone replacement therapy.

[40] Baglin, T (2004) 'Management of Thrombophilia: who to screen?' *Pathology of Haemostasis and Thrombosis* 33 401-404; Baglin, T (2001) 'Evidence-based management of deep vein thrombosis and pulmonary embolus' *Clinical Medicine* **1**(6) November/ December 348-441; Baglin C et al (1998) 'Risk of recurrent venous thromboembolism in patients with the factor V Leiden (FVR506Q) mutation; effect of warfarin and prediction by precipitating factors. East Anglian Thrombophilia Study Group. *British Journal of Haematology'* 100:764-8.

[41] Baglin, T (2007) 'Unprovoked deep vein thrombosis should be treated with long-term anticoagulation – no' *Journal of Thrombosis and Haemostasis* 5; 2336-2339.

[42] van Hylckama, VA et al (2008) 'Proof of principle of potential clinical utility of multiple SNP analysis for prediction of recurrent venous thrombosis' *Journal of Thrombosis and Haemostasis* **6**:751-754.

[43] Bauer, K 'When to Do a "Hypercoagulable Workup' ASH website *www.hematology.org/publications/hematologist/jfm04/review.cfm*

[44] The American College of Medical Genetics *Consensus Statement on Factor V Leiden Mutation Testing* (2001). College of American Pathologists *Consensus Conference XXXVI: Diagnostic Issues in Thrombophilia* (2001).

The ACMG guidelines do not comment on management of patients with FVL but the CAP guidelines do address this issue. CAP state that there is no evidence to support a different approach to managing the acute therapeutic management of VTE in patients with FVL. They state that the utility of lifelong anticoagulation for patients with FVL has not been established but that it may be recommended for patients with more than one hereditary thrombophilia (or homozygous carriers of one hereditary thrombophilia) in certain circumstances, such as FVL positive patients who have suffered an idiopathic or life-threatening VTE event. FVL carriers with no thrombotic history should receive appropriate prophylaxis when exposed to risk factors for VTE.

As would be expected, whilst the ACMG guidelines focus on the use of the genetic test, the CAP guidelines are a far broader exploration of the diagnostic options available in the detection and management of thrombophilia including when to test, and when not to test.

CAP recommendations on when Factor V testing is appropriate, offer a guide to the quality of evidence supporting different options by assigning them to one of three levels:

- Level 1 - One or more well-designed prospective study(ies) or two or more well-designed retrospective studies
- Level 2 - Retrospective studies or multiple anecdotal studies that reach consensus
- Level 3 - Isolated anecdotal studies and/or consensus of experts

- A history of recurrent VTE (Level 2)
- A first VTE at less than 50 years of age (Level 1)
- A first unprovoked VTE at any age (Level 1)
- A first VTE at an unusual anatomic site such as the cerebral, mesenteric,
- portal, or hepatic veins (Level 2)
- A first VTE, at any age, in a subject with a first degree family member with
- a VTE before age 50 (Level 1)
- A first VTE related to pregnancy, the puerperium, or oral contraceptive use (Level 1)
- A first VTE related to hormone replacement therapy (Level 3)
- An unexplained pregnancy loss during the second or third trimester (Level 2)

In the UK there is no guidance from the National Institute for health and Clinical Excellence (NICE) on the use of FVL testing, but there is widespread concern regarding one common manifestation of thrombophilia: that of Deep Vein Thrombosis (DVT) which is often accompanied by Pulmonary Embolus (PE). In the UK, this may be treated with a haemolytic therapy if patients need stabilising, but otherwise this is managed with anticoagulation therapy.[45]

At the time of writing a NICE study on prevention of DVT is being prepared. Attention has focused on the high incidence of DVT-related hospital events (at least 64,000) including more than 6500 deaths in 2004-05.[46] The NICE scoping document states that:

'There is no current worldwide consensus on which patients should receive thrombophrophylaxis. The inconsistent use of preventative measures for VTE has been widely reported. A recent UK survey suggested that 71% of patients assessed to be at medium or high risk of developing DVT did not receive any form of pharmacological or mechanical thromboprophylaxis' NICE (2007) Scope document p.3.

There is no mention in the NICE document of the role of FVL, or any other genetic loci, in

[45] Baglin, T (2001) 'Evidence-based management of deep vein thrombosis and pulmonary embolus' *Clinical Medicine* **1**(6) November/ December 348-441.
[46] http://www.nice.org.uk/nicemedia/pdf/VTEpreventionscope.pdf

screening patients for thrombotic risk factors. Table 1 puts the genetic risk factors in a wider context, as explained in the previous section on evidence that perhaps illustrates why this might be the case – there are many non-genetic factors.

Table 4: Risk factors for venous thrombosis

Procedural-related ▪ Major orthopaedic surgery to lower limb, for example hip or knee replacement ▪ Abdominal or pelvic surgery lasting more than 30 minutes under general anaesthetic ▪ Major trauma - hip fracture is associated with a very high risk of deep vein thrombosis.
Patient- related ▪ Age >40 and particularly >60 years ▪ Obesity, body mass index > 30kg/m2 and particularly >35kg/m2 ▪ Previous DVT or PE ▪ Known thrombophilia (a predisposing state which may be heritable) ▪ Malignancy ▪ Heart failure ▪ Respiratory disease ▪ Sever infection ▪ Oestrogen therapy and high dose progestens ▪ Pregnancy and the postpartum

Adapted from: Table 1 in T. Baglin Venous thromboembolism in hospitalised patients: a public health crisis' *British Journal of Haematology* 141 p.765

In Germany guidelines on thrombosis often mention FVL as a risk factor, among other hereditary factors and clinical factors. The guideline of the German Society of Surgery (Deutschen Gesellschaft für Chirurgie) and 20 other medical associations on thrombophilia in surgery and perioperative situations mentions "APC resistance/Factor V Leiden" as a risk factor for thrombophilia following surgery (DGC *et al.,*. 2003). The presence of Factor V Leiden is also mentioned as a risk factor for thrombophilia in patient with venous ulcers (DGP 2008). The German Society for General Medicin and Family Medicin (Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (2006), also mentions Factor V Leiden as a risk factor for thrombosis following a stroke.

However it appears the APC resistance test is more commonly recommended than the test for FVL. The Deutschen Gesellschaft für Phlebologie mentions FVL as a risk factor in its *Leitlinie: Diagnostik und Therapie der tiefen Bein- und Beckenvenenthrombose* (DGP, 2003), which provides clinicians with information about the diagnostic and therapy of venous thrombosis of legs and pelvis. It outlines information of prevalence of the gene variant and relative risk, but does not recommend FVL testing. A guideline on spontaneous abortion establishes FVL as a risk factor for thrombophilia in cases of such events, offering the advice that it makes sense to establish more exactly the risk but without recommending a genetic test (DGGG and AGIM, 2008).

A guideline on cerebral vein and sinus thrombosis considers it important to establish the presence of FVL in patients for measuring the risk of further manifestations of the disease following

such an event, but recommends APC resistance measurement (DGN, 2005a). The Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V. mentions both Factor V Leiden as a risk factor for thrombosis in women taking oral hormonal contraceptives, but refers to an APC resistance test instead of the FVL test (DGGG, 2008).

In the Netherlands, guidelines on thrombophilia and avoidance of thrombosis, as well as the documents on clinical utility of FVL testing refer to FVL as one among many others hereditary and acquired risk factors for such events. These risk factors also include antithrombin protein deficiency, protein C deficiency, protein S deficiency and gene variants prothrombin G20210A and Factor VIII. After mentioning the increase in risk represented by these factors for various conditions (deep vein thrombosis, pregnancy, foetal loss, use of oral contraception) phenotypic and genetic tests are discussed.

2.5.3 Practice and costs

A recent retrospective analysis of laboratory orders and results from September 2005 to August 2006 looked at doctors' ordering practices, to measure compliance with the 2002 CAP consensus guidelines which set out the limitations of thrombophilia testing. The results showed that in 2006, many physicians appeared to lack awareness of the guidelines (Jackson BR, et al. *BMC Clin Pathol.* 2008; 8:3). Second-line (antigen) tests were ordered nearly as commonly as first–line (functional) assays. Commenting on these results in a recent issue of CAP Today Dr. George Rodgers, one of the authors of the study, suggested that: "Probably half or more of these samples were taken from patients on warfarin, so they were falsely positive. A lot of money is being wasted, and a lot of misleading test results are being recorded." Dr Rodgers also highlighted the issue of patient safety: "Patients may be wrongly labelled as having a genetic disease but it is actually a laboratory mistake,".[47] This could be taken as an indication of why a genotypic test may be more suitable than a phenotypic one, however even where accurate results are given, CAP Today cites a US haematologist George M. Rodgers, at a large US reference laboratory, as stating that "most clinical data suggest that … making a diagnosis of an inherited disorder in a patient with a blood clot probably does not change long-term management."[48] This view is echoed in the UK where one clinician said that 'in probability' the test result 'doesn't change management of a patient' and that the patient with the Factor V Leiden mutation is not at higher risk of recurrence than other patients with thrombosis who have had a thrombosis (UK clinician). In the Netherlands there is a general consensus that thrombophilia screening only should be performed where it is expected that the outcome of the test will influence the management decision of the physician using evidence based guidelines, but there is continued debate on the evidence, while in practice, guideline recommendations are not strictly followed leading to overuse.

No reimbursement problems were reported in the UK, the Netherlands and Germany. Indeed one laboratory in Germany suggested it was too easy (DE lab). The costs of tests are borne by either the government or health insurance funds. A comprehensive survey of commercial kit prices was not undertaken, but a single genotype might cost £15 from a CE marked kit (EU Kitmaker), while one UK lab quoted their price to clients as being around £45. A lab in the Netherlands quoted a price of 150Euros. However it should be noted that the services may not be comparable, for example in the Netherlands one lab reports averaging its costs over all test users whether or not they require APC and FVL tests to report a full result. Labs may also combine multiple genetic risk factors in their service price.

[47] Check, W (2008) Clot knot—unraveling tests for coag disorders *CAP Today* December

[48] Check, W (2008) Clot knot—unraveling tests for coag disorders *CAP Today* December

2.5.5 Patients, doctors and the use of test results

A view put forward by UK clinicians and a UK lab was that patients want to know why they have had a thrombotic event, and that a test can offer them some form of answer. Indeed one lab suggested this might offer them a chance to change their lifestyle to reduce their risks of recurrence. However the way such information might be used in the clinic is often problematic. A UK qualitative study[49] (of 42 patients) has shown that patients who had Factor V Leiden tests used the results to inform their decisions to take HRT and oral contraceptives, and took precautions when flying. However they did not change their lifestyles to avoid other environmental triggers (e.g. diets that maintain obesity). Furthermore patients' experience of the test depended very much on how informed they were about FVL. Some were left confused and anxious, or had incorrect perceptions that may well be transmitted to other at-risk family members. The results are suggested to call into question the suitability of FVL testing in an unsupported primary care setting.[50] Similarly a survey of 110 patients tested for FVL in the US found that after test results had been explained the majority of patients felt they had not been given sufficient information about FVL. Over half felt their clinician did not understand FVL.[51]

2.6 Lessons learned on the role of IP

The patent on the FVL mutation was exclusively licensed by its public sector owner to a large firm with a diagnostics business that subsequently controlled access to sub-licenses although a number appear to have been granted, notably to kit makers. As the kit has been licensed several times it appears that the licensing costs are not unreasonable, yet it also seems that the patent has not been strictly enforced and many laboratories and some kit makers are infringing the patent.

2.6.1 Patenting and access to testing for patients

This study has found no evidence in any of the four countries studied of problems relating to the availability of the FVL tests for patients due to patents on FVL. Although this study is only exploratory it is notable that in the EU three of five labs we spoke to and at least three of four clinicians were unaware of the patented status of FVL. As a UK clinician noted "no-one talks about I.P. in the context of this assay".

Labs said that they had not been approached for royalty payments or pressed to use commercial kits (supporting the statement by the interviewee from the Patent owning institution). FVL was seen as a very simple test to undertake and it had moved rapidly into use with no delay according to several EU laboratories. The test is very widely used, even though as noted in the previous section, it often may not change the management of patients. There do not appear to have been any problems in obtaining payment from either health insurers or federal healthcare providers in the Netherlands, Germany or the UK. It was not clear whether or not this was the case in the USA. Finally, as reported in the Work Package 2 report, interviews with patient organisations in the UK, Netherlands and Germany did not find any access problems related to patenting.

2.6.2 Patenting and innovation

[49] Saukko, PM et al (2006) 'Are genetic tests exceptional? Lessons from a qualitative study on thrombophilia' *Social Science and Medicine* 63:1947-1959
[50] Saukko, PM et al (2006) 'Are genetic tests exceptional? Lessons from a qualitative study on thrombophilia' *Social Science and Medicine* 63:1947-1959
[51] Hellmann EA; Leslie ND and Moll S (2003) Knowledge and educational needs of individuals with the factor V Leiden mutation *J. Thromb Haemost* 1: 2335-9.

The FVL test was made available very rapidly by public sector labs developing their own assays, and one EU lab felt that rapid progress had been made in the field as a result, with multiple tests being available for comparison by users. The patent was widely noted not to have been enforced and this non-enforcement was viewed as having favoured in-house developed laboratory tests as laboratories developing 'home-brews' mix and match instrumentation platforms, research only reagents, commercial kits and customised reagents. Enforcement of a patent would have slowed down progress according to two EU labs.

A kit maker and a US and EU laboratory scientist thought that research on the clinical validity and utility of the FVL mutation had been done by academic researchers in Leiden and elsewhere rather than being funded by commercial organisations, although we found one study where there clearly had been some collaboration with industry. One respondent suggested that good clinical validation studies of the FVL association were carried out by Bertina and colleagues in Leiden and indeed that no other single mutation had a stronger scientific support, which had created a lot of interest in the possibilities of genetic testing as a whole (EU kit maker). However the same interviewee claimed the licensee (Organon Technica and latterly bioMérieux), had done nothing following this to build up on this initial good situation: "overall, it seems that bioMérieux made its profit out of that by doing nothing" (EU kit maker).

The assignee also had found the FVL patent to be profitable and as a consequence of this experience, they had continued to patent in the field and to add IP to their agreement with their licensee. The revenues of the FVL patent have been and are used exlusively to finance (thrombophilia) research at Leiden, it is claimed. There was some disagreement amongst other groups as one laboratory felt the patent was not a success if it could not be enforced while an EU kit maker thought a profitable outcome was successful enough for the effort made even if there were some infringers.

In contrast to the positive outcome for the licensee, assignee/patent owner and laboratories some others expressed negative sentiments. One kit-maker that had taken out a licence was disappointed that their market share was eroded because the patent was not enforced. Another kit maker had delayed launching their product over licensing concerns. This kit maker had also suffered from not being able to access platform IP to develop the test for a wider market. This same experience in accessing some platform IP (thermostable enzymes) had also affected an EU laboratory that had developed a high throughput method for detection of a range of thrombophilia-related mutations. Furthermore, concern was expressed by a US kit maker about the stacking of royalties in this field, who suggested that Universities such as Leiden may agree too high a royalty rate with licensees and that this could delay the launch of commercial kits if a high exclusive licensee burden is passed on to sub-licensees (although of course it is possible a low cost exclusive license could be sub-licensed at a high price too). Yet despite these concerns, it appears that commercial products have not been stifled in this case, as proven by the range of kits available.

2.6.3 Lessons from comparing the US and EU

The case of FVL patenting offers fewer opportunities to learn from contrasts between the US and EU than, for example, TPMT. Firstly, the patent position around FVL appears to be similar in both regions. Secondly, FVL testing is widely used in all the countries studied, despite there being evidence from each country that the test may have been over-used. Finally, there do not appear to be significant patent enforcement activities in either region to contrast.

Appendix B: Factor V Leiden (FVL)

Family	Patent	Status	Patent Number	Patent Country	Filing Date	Publication Date	Assignees	New Assignees	Inventors	Title
1	Granted	In force	EP696325B1	DE GB NL	1995-02-14	19980513	Rijks Universiteit Leiden		Rogier Maria Bertina (NL) Pieter Hendrik Reitsma (NL)	A method for screening for the presence of a genetic defect associated with thrombosis and/or poor anticoagulant response to activated protein C
1	Granted	In force	EP807691B1	DE GB NL	1995-02-14	20011010	Rijks Universiteit Leiden		Rogier Maria Bertina (NL) Pieter Hendrik Reitsma (NL)	A method for screening for the presence of a genetic defect associated with thrombosis and/or poor anticoagulant response to activated protein C.
1	Granted	In force	US6518016B1	US	1995-06-06	20030211	Rijks Universiteit Leiden		Rogier Maria Bertina (NL) Pieter Hendrik Reitsma (NL)	Method for diagnosing an increased risk for thrombosis or a genetic defect causing thrombosis and kit for use with the same

1	Granted	In force	US5874256A	US	1997-02-21	19990223	Rijks Univer-siteit Leiden		Rogier Maria Bertina (NL) Pieter Hendrik Reitsma (NL)	Method for diagnosing an increased risk for thrombosis or a genetic defect causing thrombosis and kit for use with the same
1	Granted	In force	US6558913B1	US	1998-09-30	20030506	Rijks Univer-siteit Leiden		Rogier Maria Bertina (NL) Pieter Hendrik Reitsma (NL)	Method for screening for the presence of genetic defect associ-ated with thrombosis and/or poor anticoagulant response to activated pro-tein C
2	Filed	PCT App. Not Ent. Europ. Phase	WO1997032040A2	DE GB US NL	1997-02-27	19970904	Royal Infirmary Of Edinburgh NHS Trust		STIRLING, David LUDLAM, Christopher, Armstrong	Nucleic acid sequence detection
3	Filed	RO Processing Completed-Placed In Storage	WO1997046714A1	DE GB US NL	1997-06-04	19971211	University Of Utah Research Foundation		WITTWER, Carl, T. RIRIE, Kirk, M. RASMUSSEN, Randy, P.	Monitoring hybridization during pcr
3	Filed	First Examina-tion Report	EP0912766	DE GB NL	1997-06-04	19990506	University Of Utah Research Foundation		WITTWER CARL T [US] ; RIRIE KIRK M [US] (+1)	Monitoring hybridization during pcr

4	Granted	In force	US6277570B1	US	1998-09-04	20010821	NAXCOR [US]	Thien, Douglas	WOOD MICHAEL L [US] ; ALBAGLI DAVID [US] (+4)	Nucleic acid sequence detection employing probes comprising non-nucleosidic coumarin derivatives as polynucleotide-crosslinking agents
4	Granted	In force	US6495676B1	US	1999-09-03	20021217	NAXCOR [US]	Thien, Douglas	WOOD MICHAEL L [US] ; ALBAGLI DAVID [US] (+4)	Nucleic acid sequence detection employing probes comprising non-nucleosidic coumarin derivatives as polynucleotide-crosslinking agents
4	Granted	Expired	US6737239B2	US	2002-10-15	20040518	NAXCOR [US]	Thien, Douglas	WOOD MICHAEL L [US] ; ALBAGLI DAVID [US] (+4)	Nucleic acid sequence detection employing probes comprising non-nucleosidic coumarin derivatives as polynucleotide-crosslinking agents
5	Granted	In force	US6451526	US	1999-01-15	20020917	Mayo Foundation For Medical Education And Research, US		Lu Song, Dennis J. O'Kane, Kelly L. Krajnik, John A. Heit,	Simplified mutation detection

5	Filed	The application is deemed to be withdrawn	WO9936574 A1	DE GB NL	1999-01-15	19990722	Mayo Foundation For Medical Education And Research, US		SONG, Lu O'KANE, Dennis, J. KRAJNIK, Kelly, L. HEIT, John, A.	Simplified mutation detection
6	Filed	EP Withdrawn 20060103	WO1999064626A2	DE GB US NL	1999-06-04	19991216	Genostic Pharma Limited		ROBERTS, Gareth, Wyn	Probes used for genetic profiling
6	Filed	Abandoned -- Failure to Respond to an Office Action	US20030198970A1	USA	2002-07-29	20031023	Genostic Pharma Limited		ROBERTS, Gareth Wyn, Cambs (GB)	Genostics
7	Filed	PCT - International Search Report Mailed to IB	WO2000017383A1	DE GB NL	1999-08-24	20000330	Nexstar Pharmaceuticals, Inc.		BRODY, Edward, N. GOLD, Larry	Factor V leiden detection
8	Granted	Expired	US6270973B1	US	1999-09-27	20010807	Promega Corporation		Martin K. Lewis, Daniel Kephart, Richard Byron Rhodes, John William Shultz, Donna Leippe, Michelle Mandrekar, Christine Ann Andrews, James Robert Hartnett, I Trent Gu, Keith V. Wood, Roy Welch	Multiplex method for nucleic acid detection

8	Filed	PCT - Docketed Chapter 1 Case	WO2000049181A1	DE GB NL	2000-02-18	20000824	Promega Corporation		LEWIS, Martin, K. KEPHART, Daniel RHODES, Richard, B. SHULTZ, John, W. LEIPPE, Donna MANDREKAR, Michelle ANDREWS, Christine, Ann HARTNETT, James, R. GU, Trent WOOD, Keith, V. WELCH, Roy	Multiplex method for nucleic acid detection
8	Granted	In force	US6653078	US	2001-02-20	20031125	Promega Corp (US)		Martin K. Lewis, Daniel Kephart, Richard Byron Rhodes, John William Shultz, Donna Leippe, Michelle Mandrekar, Christine Ann Andrews, James Robert Hartnett, Trent Gu, Keith V. Wood, Roy Welch	Multiplex method for nucleic acid detection
9	Granted	Lapsed	US6248548B1	US	1999-11-01	20010619	The University of Vermont and State Agriculture College		Cornelis Van't Veer, Michael Kalafatis, Kenneth G. Mann	Thrombosis prophylaxis for factor Vleiden carriers

10	Granted	In force	US6479242	US	2000-10-27	20021112	Univ State Cleveland (US)		Baochuan Guo, Xiyuan Sun	Method for genotyping of single nucleotide polymorphism
11	Filed	PCT App. Not Ent. Europ. Phase	WO2003064687A2	DE GB US NL	2003-01-28	20030807	Imperial College Innovations Limited|Thomas, Howard|Hill, Adrian|Wright, Mark|Thursz, Mark		THOMAS, Howard (GB) HILL, Adrian (GB) WRIGHT, Mark (GB), THURSZ, Mark (GB)	Methods
12	Filed	PCT - International Search Report Mailed to IB	WO2003074740A1	DE GB NL	2003-02-28	20030912	Dhallan, Ravinder		DHALLAN, Ravinder	Rapid analysis of variations in a genome
12	Granted	In force	US7208274	US	2003-02-28	20070424	Dhallan Ravinder S (US)		DHALLAN, Ravinder	Rapid analysis of variations in a genome
12	Filed	PCT - International Search Report Mailed to IB	WO2003074723	DE GB US NL	2003-02-28	20030912	Dhallan, Ravinder [US/US]		DHALLAN, Ravinder	Methods for detection of genetic disorders
12	Filed	First Examination Report 20070514	EP1481092	DE GB NL	2003-02-28	20030912	Ravgen Inc (US)		DHALLAN RAVINDER [US]	Methods for detection of genetic disorders
12	Filed	First Examination Report 20070514	EP1481097	DE GB NL	2003-02-28	2004-12-01	Ravgen Inc (Us)		DHALLAN RAVINDER [US]	Rapid analysis of variations in a genome
12	Filed	PCT - International Search Report Mailed to IB	WO2004078994A2	DE GB US NL	2004-03-01	20040916	Ravgen, Inc.|Dhallan, Ravinder		DHALLAN, Ravinder	Methods for detection of genetic disorders
12	Filed	Final Rejection Mailed	US20060121452A1	US	2005-08-26	20060608	Ravgen, Inc.		DHALLAN, Ravinder S.	Methods for detection of genetic disorders
13	Filed	Abandoned -- Failure to Respond to an Office Action	US20050261688A1	US	2003-12-12	20050203	Genesis Group Inc (CA)		XIE, Ya-Gang	Method for the detection of risk factors associated with myocardial infarction

13	Filed	Non Final Action Mailed	US2006252084A1	US	2006-07-05	20061109	Genesis Group Inc (CA)		XIE, Ya-Gang (CA)	Method for the detection of risk factors associated with myocardial infarction
14	Filed	Supplementary Search Report 20080604	WO2005047533A1	DE GB US NL	2004-11-17	20050526	TM Bioscience Corporation		BORTOLIN SUSAN (CA) ; MERANTE FRANK [CA] KOBLER, Daniel (CA) FIELDHOUSE, Daniel (CA) BLACK, Margot (CA) MODI, Hemanshu (CA) ZASTAWNY, Roman (CA) JANECZKO, Richard, A. (CA)	Method of detecting mutations associated with thrombosis
15	Filed	Application Undergoing Preexam Processing	WO2005071114A1	DE GB US NL	2005-01-14	20050804	The Government Of The United States Of America As Represented By The Secretary Of The Department Of Health And Human Services		DOGULU, Cigdem, F. (US) RENNERT, Owen, M. (US) CHAN, Wai-Yee (US)	Method evolved for recognition of thrombophilia (mert)
16	Filed	Abandoned -- Failure to Respond to an Office Action	US20060257883A1	US	2005-05-10	20061116	{n/a}		BJORAKER, David G. [US], MELKER, Richard J. [US], DENNIS, Donn Michael [US]	Detection and measurement of hematological parameters characterizing cellular blood components

16	Filed	Application Undergoing Preexam Processing	WO2006121590A1	DE GB US NL	2006-04-21	20061116	University Of Florida Research Foundation, Inc.		BJORAKER, David, G. [US] MELKER, Richard, J. [US] DENNIS, Donn, Michael [US] MARTIN, Charles, R. [US] STEWART, Jon, D. [US]	Detection and measurement of hematological parameters characterizing cellular blood components

III. TPMT

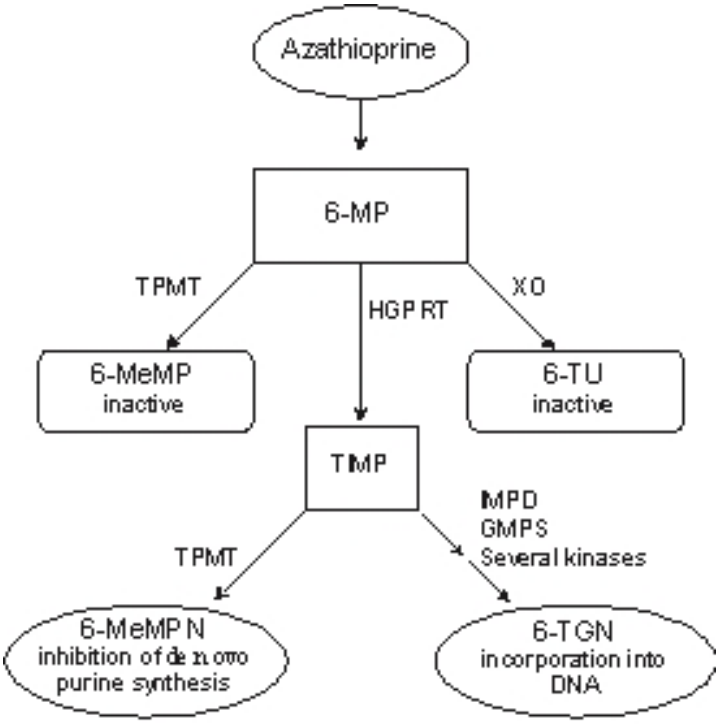
3.1 Introduction

Thiopurine drugs have been developed since the early 1950s but it was not until the 1990s that some saw potential for the use of tests to guide treatment decisions. Although the relationship between TPMT deficiency and neutropenia was quickly proved, the utility of TPMT testing in clinical practice has been much more difficult to agree between stakeholders. The cost-effectiveness of TPMT testing is also still the subject of inquiry. In the meanwhile an inestimable amount of research time, effort and money has been invested in seeking to elucidate the clinical utility of TPMT testing and uptake of the test is limited. The TPMT case is the one which most resembles the BRCA/Myriad case in so far as Prometheus, the company holding the key patents, has commercialised the test as an LDT and has sought to prevent other labs from performing the test.

3.2 Biological background

A number of thiopurine drugs have been developed since the early 1950s. These include 6-Mercaptapurine (6-MP) and 6-Thioguanine (6-TGN), licensed in the US and EU for the treatment of different types of leukemia, such as Acute Lymphocytic/ lymphoblastic Leukemia (ALL) and Azathioprine, licensed for use as an adjunct therapy to prevent renal transplant rejections, to reduce the symptoms of rheumatoid arthritis and for treatment of patients with chronic inflammatory bowel disease (the latter being a major indication of Azathioprine worldwide).[52]

[52] See also IPTS (2006) Pharmacogenetics and Pharmacogenomics: State-of-the-art and Potential Socio-economic Impact in the EU. EC-JRC, Seville. Spain.



Source: Figure 1. Imuran Product information sheet[53]

As shown in Figure 1 Azathioprine is a pro-drug that is converted into 6-MP. 6-MP is metabolized by TPMT and several other enzymes. Thiopurines' therapeutic effect is by providing 6-TGN for incorporation into DNA during DNA synthesis. This adversely effects the growth of rapidly dividing cells, including those of the immune system and certain cancers. An alternative pathway, mediated by TPMT diverts metabolites away from the supply of 6-TGN, producing 6-MeMP instead. In most individuals both 6-TGN and 6-MeMP are produced and a therapeutic effect depends on obtaining a sufficient concentration of 6-TGN.

TPMT is a cytoplasmic enzyme found in liver cells and circulating blood cells, isolated by Richard Weinshilboum and colleges (see Woodson et al.1982)[54]. Its role in metabolic pathways for thiopurine drugs had been studied since the 1960s (Krynetski and Evans 2003).[55] Weinshilboum's group subsequently cloned the gene, described in a patent application in 1994 (see next section). In 1995 Krynetski et al. working at the St. Jude Children's Research Hospital, identified, and filed patent applications on, specific polymorphisms associated with inactivation of the gene and potentially life-threatening adverse reactions resulting from reduced or abolished metabolism of thiopurine drugs into 6-MeMP (see Kryetski et al. 1995). Adverse events resulting from these include bone marrow toxicity and associated leucopenia, transaminitis, and elevated risk of lymphoma. These effects are dose-related and so are not necessarily limited to those individuals who are homozygous for polymorphisms in the TPMT gene (Seidman et al. 2006)[56].[57] Indeed some

[53] Available at http://www.drugs.com/pro/azathioprine.html accessed November 2008.
[54] Woodson LC; Dunnette JH and Weinshilboum RM (1982). *J. Pharmacol. Exp. Ther.*, **222**, 174–181.
[55] Krynetski, E and Evans WE (2003) Drug methylation in cancer therapy: lessons from the TPMT polymorphism *Oncogene* 22, 7403–7413
[56] Seidman, E; Dubinsky, M and Sandborn W (2006) 'Optimizing thiopurine response in IBD: The clinical utility of TPMT testing and metabolite monitoring' *Gastroenterology and Hepatology* 2 (8) Supplement 6.

heterozygotes may tolerate thiopurine therapy for extended periods of time before having an adverse event (ibid). Around 90% of the population have high activity, 10% intermediate activity (due to heterozygosity) and 0.3% are homozygous for TPMT deficient copies of the gene, and therefore exhibit very low or no detectable enzyme activity.[58]

3.3 TPMT patents and key assignee exploitation strategies

By the late 1990s thiopurine drugs were widely used and generically produced but some saw commercial potential not only in the manufacture of these drugs but also in facilitating their clinical use by using tests to provide further guidance for the safe and effective use of thiopurines.

This section describes how Prometheus Laboratories Inc., a US speciality pharmaceutical firm, obtained access to a suite of technologies with applications for optimising dosage regimes for patients taking thiopurine drugs and protected by three patent families - as listed in Table 1. Notably absent from Table 1 are a number of patents and patent applications filed by a range of organisations related to TPMT and a variety of applications. These are listed in Annex A, but this case-study focuses on those deemed to be of core importance at the present time to explaining current patterns of development and clinical use. Notably absent from our account here is the US patent (5,470,737) that claims the gene for the wild-type sequence to TPMT. This was filed by Weinshilboum's group in 1994 and granted in 1995 to the Mayo Foundation (for the Mayo Clinic, a large US non-profit medical clinic and research organisation where TPMT was originally isolated). We have not addressed the question of why this patent has not played a larger part in the subsequent events, other than noting that the patent claims do not explicitly mention diagnostic applications. Sections 2.1-2.3 detail the main patents that this case focuses on.

3.3.1 A test to determine the TPMT genotype of patients

The first patent family in Table 1 contains a patent granted in 1999 to the St. Jude Children's Research Hospital. US patent 5,856,095 claims three polymorphisms in the TPMT gene, and assays and kits for detecting these using a PCR-based molecular genetic method. This was based on work relating to TPMT's relevance in the treatment of children with Leukaemia. Despite a PCT filing for non-US patents made in 1997, these patent applications were allowed to lapse after 30 months. Thus there are no European patents in this patent family. In 2000 an exclusive license was agreed between St Jude and PPGX, a small biotechnology company offering services to pharmaceutical firm. The signing of an exclusive license after the 30 month PCT window for international patent applications suggests these applications were allowed to lapse due to the absence of a licensee willing to pay for these costs. The deal between PPGX and St. Jude may have benefited shareholders of PPGX as in the same year it was acquired by DNA Sciences, another a small biotechnology company, with a focus on clinical test development. In 2001 DNA Sciences initiated a commercial agreement with Prometheus Laboratories Inc., granting Prometheus a sublicense to the St. Jude patent, although DNA Sciences had already commenced TPMT testing for clinical use by 2001.[59] DNA Sciences filed for Bankruptcy in 2003, and was purchased by Genaissance (now itself owned by Clinical Data Inc., Newton, MA). It appears that Prometheus had gained a license, perhaps from the Bankruptcy court, and that that Genaissance allowed Prometheus to expand the terms of that license, extending the therapeutic areas that they could apply the test to (Genaissance press release). Due to the changing ownership of the

[57] Other side effects such as allergic reactions are not dependent on dosage and are not predictable by testing TPMT status (round table 2006).
[58] Krynetski, E and Evans WE (2003) Drug methylation in cancer therapy: lessons from the TPMT polymorphism *Oncogene* 22, 7403–7413
[59] http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/story/06-18-2001/0001515959&EDATE=

IP it is not possible to determine how or by whom, but Specialty Labs (Valencia, Calafornia)[60] was also granted a sublicense.

The terms of the St. Jude license are confidential and cannot be reported here.

3.3.2 A test to determine the concentration of thiopurine metabolites in patient blood

The second patent family in Table 1 contains two US patents and an application for a patent in 19 European states, granted by the EPO to the Canadian Hopital-Sainte-Justine.[61] These claim a method for monitoring the levels of thiopurine drug metabolites as extracted from patient blood after drug treatment has commenced. As shown in Figure 1 the metabolism of thiopurines results in the production of both 6-TGN and 6-MeMP, but polymorphisms in TPMT can lead to higher ratios of 6-TGN to 6-MEMP and associated side-effects. In these patents methods to detect the ratio of thiopurine metabolites are proposed to offer the opportunity to monitor not only for potential toxicity but also to ensure a therapeutically effective dose of drug is being delivered – hence these are offered as safety and efficacy optimising tests. In this case Prometheus actually obtained an exclusive license to the technology at the application stage, i.e. before the first of St-Justine's patents issued. Prometheus is the exclusive worldwide licensee of this technology. [62]

3.3.3 A phenotypic test of the metabolic effectiveness of a patient's TPMT enzymes

The third and final patent family in Table 1 relates to a family of patents owned by Prometheus. The first application was filed in 2001 with patents granted in 2003 and 2006. This family also has European coverage, granted by the EPO in 2008, although it appears at the time of writing that fee payments are only being maintained in the Britain, not DE and NL. The methods claimed are for determining TPMT activity after taking a sample of blood from a patient and reacting this with a thiopurine to ascertain the activity of the patient's enzymes. The claims for the method specifically mentions applications for the test in inflammatory bowel disease although the second US patent extends the range of experimental methods for determining the phenotype.

3.3.4 Other patents relating to TPMT (see Annex B)

Finally, it is noteworthy that other institutions are also interested in TPMT but have been less active thus far, and their patents and applications are detailed in Annex A. Examples include Sangamo BioSciences (a US Biotech company) who was granted a US patent in 2003 that claims a method for detecting changes in TPMT gene expression, and other specified drug metabolising enzymes as part of a panel test, following administration of a drug. Additionally the Biologix Research Company (a US equipment and reagent supplier) hold a US patent (6,946,258) on a method for measuring 6-MMP using an antibody based test.

[60] http://www.specialtylabs.com/
[61] Since the analysis was completed further US patents have issued in this patent family, including most recently patents number 7,425,546 and 7,429,570 issued in September 2008.
[62] Prometheus Laboratories Press release 11/04/2002 – www.recap.com

Table 6. TPMT-related patents owned by or licensed to Prometheus Laboratories Inc.

Family	Patent	Status in mid 2008	Patent Number	Countries covered*	Assignee	Title
1	Granted	In force	US5856095A	US	St. Jude Children's Research Hospital	Identification of two novel mutant alleles of human thiopurine S-methyltransferase, and diagnostic uses thereof
1	Filed	PCT - International Search Report Mailed to IB	WO1997007201A1	DE GB NL US	St. Jude Children's Research Hospital	Identification of two novel mutant alleles of human thiopurine s-methyltransferase, and diagnostic uses thereof
2	Granted	In force	US 6355623	US	Hopital-Sainte-Justine (Montreal, CA)	Method of treating IBD/Crohn's disease and related conditions wherein drug metabolite levels in host blood cells determine subsequent dosage
2	Granted	In force	US 6680302	US	Hopital-Sainte-Justine (Montreal, CA)	(Continuation of above patent)
2	Granted	In force	EP 1115403B1	DE GB NL	Hopital-Sainte-Justine (Montreal, CA)	Method for optimizing the use of 6-mercaptopurine in the treatment of immune-mediated gastrointestinal disorders
3	Granted	In force	US6576438B2	US	Prometheus Laboratories, Inc.	Method of determining thiopurine methyltransferase activity
3	Granted	In force	US7138250B2	US	Prometheus Laboratories, Inc.	Method of determining thiopurine methyltransferase activity
3	Granted	In force	EP1285085B1	DE GB NL	Prometheus Laboratories, Inc.	Method of determining thiopurine methyltransferase activity

* This analysis only focuses on patent coverage in four countries. Patents in other countries have not been mapped.

An important contextual detail is that TPMT tests represent approximately ~10% of sales at Prometheus Laboratories and that Prometheus has been profitable for several years. Indeed Prometheus is a business with two distinct revenue generating focuses. Its speciality pharmaceutical business focuses on gastrointestinal, autoimmune and inflammatory disorders. This generates the majority of its sales. One of the drugs Prometheus sells is a branded generic version of Azathioprine, named Imuran. It is important to note that Prometheus does not actively market Imuran and that Azathioprine is not licensed for applications other than as an adjunct therapy to prevent renal transplant rejections and to reduce the symptoms of Rheumatoid Arthritis as noted

in Section 1 above. Prometheus also have a dedicated CLIA laboratory offering a range of tests, several of which relate to TPMT, as a recent 2008 press release notes[63]:

"Combined, Prometheus' thiopurine management diagnostic tests – PROMETHEUS® TPMT Genetics and PROMETHEUS® TPMT Enzyme for individualizing dosing before therapy, and PROMETHEUS® Thiopurine Metabolites for optimizing dosing during therapy – provide information that helps physicians better manage therapeutic treatment, achieve better clinical outcomes and lower the potential for toxicity" Prometheus Laboratories (2008)

Prometheus's strategy thus far has been to provide a laboratory testing service for TPMT rather than developing a kit for use in outside laboratories.

Another diagnostic kit manufacturer speculated on the case of TPMT and Prometheus's choice of strategy suggesting no kits had been made available because of the combination of two factors (i) costs for FDA approval, thought to exceed $2m and (ii) a royalty burden agreed at too high a level, possibly because neither party had much experience of structuring such deals:

"TPMT is a fascinating sort because the FDA and the Bureau of Drugs have for years wanted a diagnostic manufacturer to develop a product for that thing and no manufacturer is going to do it because they can't afford the royalty burden….its sort of counterintuitive, the FDA… they press the manufacturers to make regulated products [the FDA say] 'we want it in a kit, we want you to commit' and all this kind of stuff, but when you get into looking at… the licensing environment what it actually encourages, in some cases such as this one, it actually encourages the labs to do homebrews and then there's no consistency, there's no regulatory oversight other than through CLIA and so the FDA certainly isn't getting their goals met for having a registered product."

Instead Prometheus' strategy seems to be to us a sales force (of around 180) to promote TPMT testing in support of US gastroenterologists who widely prescribe thiopurines, particularly in the treatment of Crohn's disease. This is cost effective for Prometheus as these clinicians also prescribe Prometheus's other products (e.g. Lotronex for management of Irritable Bowel Syndrome). It appears that Prometheus is not promoting TPMT tests to clinicians beyond Gastroenterology. This is likely to be because sales forces are expensive to train and maintain and so unless these costs are met with sufficient sales revenues (less likely in fields where Prometheus has fewer products) then Prometheus is unlikely to have an incentive to invest in such efforts.

Materials on the Prometheus website indicate they are active in providing information to health providers and insurers, marketing the TPMT tests and supporting studies by academic research groups to further advance the knowledge base around TPMT. A limitation of this case study is that it has not provided an analysis of the relative investments made by different institutions in the evidence base for TPMT testing. However it is apparent that Prometheus has been an active investor in studies generating at least six academic papers directly (focusing on early stage R&D, such as proof of concept studies), as well as supporting the research of others collaborating academic groups, as evident from licensing agreements.[64]

3.3.5 Enforcement in the USA

Prometheus has invested in at least two IP licenses related to thiopurine drug metabolism and has therefore been keen to enforce their intellectual property rights. In the US they have issued

[63] http://phx.corporate-ir.net/phoenix.zhtml?c=130685&p=irol-newsArticle&ID=1219877&highlight=

[64] Prometheus is mentioned in the address of 6 publications on (as found with a search for thiopurine* on ISI Web of Science 4th December 2008).

cease and desist letters and are involved in litigation, with one dispute settled and two in progress.

Following filing of a lawsuit by Prometheus, settlement was reached with Speciality Laboratories Inc. in 2004 due to alleged infringement of Prometheus's exclusive license for the thiopurine metabolite monitoring test. According to their website, Speciality Laboratories continue to offer this test as a 'send-out' service (i.e. Prometheus undertake the test on their behalf).[65] The same test has also been the subject of litigation with the Mayo Clinic, again due to alleged infringement of the metabolite monitoring patent by Mayo.

In March 2008, in ***Prometheus v Mayo*** the Southern District Court of California found that the two St. Justine patents in question were invalid because they are based on claims for natural phenomena i.e. the correlation between the concentration of a drug and a toxic or therapeutic effect. In the same year the case was taken by Prometheus to the federal court circuit and the dispute continues.[66]

Prometheus also filed a lawsuit against Quest Diagnostics Inc. (a large US private clinical test provider) for allegedly infringing the genotypic test but this case was initially dismissed in 2007 on grounds that, as a sub-licensee, Prometheus did not have standing with the court. [67] Subsequently St. Jude have entered this dispute to enforce their patent.[68]

3.3.6 Enforcement in the EU

So far Prometheus has not been active in enforcing their intellectual property rights in the EU. This is evident from comments by several EU laboratories who have not been notified of any patent infringement.

EU laboratories reported being aware of patents around either TPMT genotyping or phenotyping, even beyond those in Table B. Yet of six different EU laboratories and a kit manufacturer, only one interviewee did not have difficulty accurately describing the patent coverage relevant to their context.

The responses of the six remaining are as follows. One EU laboratory director who employs the phenotypic test, had seen a patent application for this test had dismissed it. They could not understand how this patent had subsequently been granted on an enzyme test they suggested was composed of steps that existed in the prior art (citing the publications of other laboratories to support this claim). They also expressed scepticism about the patent's value, given that the lab director claimed to be using similar method that was not covered by the patent and the perceived high cost of enforcement. Another EU laboratory director who was an occasional user of the DNA test assumed (wrongly) that Prometheus had a patent on the DNA test in the EU but not the phenotypic test. A third laboratory director, who used the DNA test, also presumed that Prometheus had licensed a European patent on genotyping. They reacted by first delaying and then limiting their own service for the test. They also made it available at no cost, and then at minimum cost. When they discovered another potential patent problem (The Schwab application covering rare mutations - as a result of being asked to participate in this study) this made them consider returning to a no-fee service. The laboratory director suggested they would be willing to license the test but only if it did not result in their price being pushed higher than the current price of ~80 €. Another

[65] http://www.specialtylabs.com/tests/details.asp?id=S50395
[66] http://www.patentdocs.net/patent_docs/2008/09/biotech-cases-t.html
[67] Holman, C (2008) The Impact of Human Gene Patents on Innovation and Access: A Survey of Human Gene Patent Litigation. February 19 *Berkeley Center for Law and Technology. Law and Technology Scholarship (Selected by the Berkeley Center for Law & Technology)*. Paper 43. http://repositories.cdlib.org/bclt/lts/43
[68] http://dockets.justia.com/docket/court-tnwdce/case_no-2:2008cv02299/case_id-50388/

laboratory concluded patents had not had an impact on what they did and decisions to conduct research on the clinical performance and clinical utility of the test had been unaffected, although they thought the kit they purchased was based on a patent. One laboratory director that was not aware of patents on TPMT gene variants believed patent enforcement in their country to be lax (EU LAB1). Finally the EU kit maker thought the situation to be quite unclear about which patents were in force in Europe.

3.4 TPMT test availability and usage

Tests related to TPMT may be used to support prescribing across a range of disorders and in many different countries. A limitation of this case study is that it focuses mainly on gastroenterology in the US and EU, although the authors have previously focused on TPMT testing for ALL, this is a relatively small field compared to gastroenterology where much TPMT testing has been conducted within large research studies, hence this is not further discussed here.[69] However where possible some comparisons have been made with other disease areas.

3.4.1 TPMT test availability and usage (USA)

US clinicians have a range of tests at their disposal to support the prescribing of thiopurine drugs including a genetic test that directly screens for known mutations in the TPMT gene, a phenotypic test that can detect actual enzyme activity levels, and a metabolite monitoring test that can be used to track drug metabolism in patients during treatment. In addition, the label for Imuran specifically states that full blood counts are recommended to reveal the extent to which patients are reacting to treatment, and that TPMT testing is not a substitute for this key indicator of potentially serious haematological side-effects.[70]

The PCR-based DNA test for specific polymorphisms in the TPMT gene has been available in the US since the mid 1990s [71] and it was rapidly shown through research in several centres that a relatively small number of mutations account for ~95% of inherited TPMT deficiency in population.[72]

TPMT-related tests appear to be widely available in the USA, from Prometheus and laboratories such as Speciality Laboratories, and the Mayo Clinic who send samples to Prometheus[73], as well as from other private laboratories who operate their own service, despite the threat of litigation, such as Quest. One laboratory (US lab1) indicated at interview they had not launched a genotypic test due to the patent position, but after some years of delay had developed, very recently, their own phenotypic test which, based on legal advice they believed did not infringe Prometheus's intellectual property.

Nonetheless, the extent of TPMT test usage in the US is difficult to determine. Yip et al. undertook a survey of 145 US gastroenterologists (which is only a small sample of the total suggested by interviewees to be over 11,000). These were also based on a subset interested in attending

[69] See IPTS (2006) Pharmacogenetics and Pharmacogenomics: State-of-the-art and Potential Socio-economic Impact in the EU. EC-JRC, Seville. Spain, and Woelderink, A., Ibarreta, D., Hopkins, M.M. & Rodriguez-Cerezo, E. The current clinical practice of pharmacogenetic testing in Europe: TPMT and HER2 as case studies. *Pharmacogenomics J.* **6**, 3–7 (2006).

[70] Available at http://www.drugs.com/pro/azathioprine.html accessed November 2008.

[71] Yates, C et al. (1997) 'Molecular Diagnosis of thiopurine S-methyltransferase deficiency: genetic basis for azathiopurine and mercaptopurine intolerance' *Annals of Internal medicine* Apr. 126(8):608-14.

[72] Krynetski, E and Evans WE (2003) Drug methylation in cancer therapy: lessons from the TPMT polymorphism *Oncogene* 22: 7403–7413

[73] http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/91565 accessed 20/04/09

certain events). They found clinicians use blood counts more than testing for TPMT levels or monitoring.[74] Indeed only 35% reported using TPMT testing while 46% used metabolite monitoring (58% of those checking metabolites also tested TPMT activity levels, and 75% of those using tests of TPMT levels also used metabolite monitoring). Yet 50% of gastroentrologists who chose to start patients at full doses of Azathioprine, rather than using a dose escalation strategy, did so without offering their patients a TPMT test.[75] Clinicians who tested for TPMT were more likely to start their patients at a full dose, which could yield more rapid therapeutic benefit for their patients when dosed safely.[76]

There are also clearly still debates within the clinical community over which tests to use. Some suggest phenotyping gives results that are more useful for dosing intermediate metabolisers than genotyping and, as a direct test of the metabolism is better (US clinician).[77] However the US clinician interviewed did not use the test often and thought that clinical trials were needed to show the utility of any form of TPMT testing in the context of Crohn's disease. Yip et al. noted that there were no expert guidelines on how to use TPMT or metabolite monitoring for gastroenterologists,[78] and the US clinician interviewed suggested that although the FDA and AGA guidelines suggested a test should be used it was still unclear how to act on the results.

Furthermore the US clinician suggested "it takes a week to get back results, that's one thing so it's a long delay…that to me is a problem. Its also very expensive [they suggested over $300] and many insurance companies don't pay for it…that's why I don't use it very frequently" (US Clinician).

This view was echoed by the US laboratory interviewed, who suggested that clients wanted to choose which laboratory provided the service and that Prometheus's test was too expensive. Yip et al. also note that many gastroenterologists had difficulty in using tests due to reimbursement issues with insurers, and also on test availability, although they did not determine the impact of these factors. It is not possible to determine if these views are representative in this study.

A commercial provider can of course argue that their test is more expensive because of the costs of maintaining the sales force that sells it and that this information provision allows the test to diffuse where it otherwise might not do so as quickly. It may also be argued that a specialist lab focusing on the test will have better expertise in provision of that test than some other providers and that this will have implications for the quality of the test they can produce.

It should be noted that there is a global quality assurance scheme for TPMT testing laboratories which may mitigate this concern to some extent. Indeed a US laboratory suggested "The flip side of this [monopoly on testing] is that with only one laboratory performing testing, patients' cannot get a 'second opinion' or be able to judge the quality of the testing."

Indeed the Mayo clinic website details for their send-out service for the Prometheus test seem to suggest that this test focuses on three mutations only,[79] which is a less extensive test than some European tests (see below).

[74] Yip JS et al (2008) how are Azathioprine and 6-Mercaptopurine dosed by Gastroenterologists? Results of a survey of clinical practice *Inflamm Bowel Dis* 14(4) April. 514-518.
[75] Yip JS et al (2008) how are Azathioprine and 6-Mercaptopurine dosed by Gastroenterologists? Results of a survey of clinical practice *Inflamm Bowel Dis* 14(4) April. 514-518.
[76] Yip JS et al (2008) how are Azathioprine and 6-Mercaptopurine dosed by Gastroenterologists? Results of a survey of clinical practice *Inflamm Bowel Dis* 14(4) April. 514-518.
[77] Seidman et al. 2006.
[78] Yip JS et al (2008) how are Azathioprine and 6-Mercaptopurine dosed by Gastroenterologists? Results of a survey of clinical practice *Inflamm Bowel Dis* 14(4) April. 514-518.
[79] http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/91565 accessed 20/04/09

3.4.2 TPMT test availability and usage (EU)

Azathioprine is a widely used drug in the EU, as indicated by a survey recording that 99% of responding English clinicians in Dermatology, Rheumatology and Gastroenterology prescribe it.[80]

In the EU there as been little commercial investment behind TPMT testing,[81] By contrast Prometheus has clearly made a substantial investment in licenses, R&D and market shaping.

Compagni et al. suggest there are at least 24 laboratories conducting TPMT genotyping in the EU, but indicated that these processed no more than 300 of these tests per year.[82] However a number of laboratories also offered phenotypic testing, which was indicated as a necessary complement to the genotypic test. Some other laboratories focused on the phenotypic enzyme test, using the genotypic test only to confirm the presence of specific mutations.

This case study focuses only on Germany, the Netherlands and the UK and finds indications of strong differences between them in the uptake of TPMT-related laboratory services.

A small number of laboratories were identified as offering TPMT tests in each of the countries studies. Several commercial kit producers were also identified, although previous research found almost all EU laboratories surveyed use homebrews rather than kits.[83] Comparative prices for all TPMT tests were not gathered but as an illustration, kits in Europe have been suggested as costing laboratories 20-30€ per test unit for genotypic kits. An average of 68€ for a genotypic test is typical for a laboratory service, and in the countries where insurance reimbursement is above the cost of the test, this averaged 188€.[84] This compares with a price of over 400€ for Prometheus's test, as quoted by Dubinsky et al. (2005) cited in Compagni et al. (2008). It therefore appears Prometheus's test is twice as expensive as those offered in EU laboratories. However it should be noted that all lab test prices are likely to vary from list prices.

Qiagen/Artus manufacturer a CE-marked *artus*® TPMT LC PCR Kits. (Compagni *et al.*, 2008; Qiagen 2007), while it seems ImmunDiagnostik AG, stopped offering such kits because of lack of market interest. Biologix also offer a CE-marked immunodiagnostic kit.[85] Applied Biosystems also offer a test that detects TPMT mutations together with numerous other drug metabolizing enzymes. However this is not licensed for clinical use. German producers of azathiopurine collaborated for a period with a German hospital laboratory to offer, as a free trial, phenotyping as a companion to their therapeutic (EU clinician and EU lab director).

In Germany two laboratories reported low demand for testing even though the test was reportedly widely available. This was suggested to be because of a lack of awareness amongst clinicians rather than due to patent related issues. However a German clinician and a laboratory said that TPMT is not currently reimbursed by health insurers there, citing that the test could only explain 30-50% of toxicity cases.

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[80] Fargher EA et al (2007) Current use of pharmacogenetic testing: a national survey of thiopurine methyltransferase testing prior to azathioprine prescription *Journal of Clinical Pharmacy and Therapeutics* 32(2):187-95.
[81] Hopkins, M et al (2006) 'Putting pharmacogenetics into practice' *Nature Biotechnology* 24(4): 403-410.
[82] Compagni A (2008) Avoiding adverse drug reactions by pharmacogenetic testing : A systematic review of the economic evidence in the case of TPMT and AZA-induced side effects. *International Journal of Technology Assessment in Health Care* 24(3): 294-302.
[83] Compagni A (2008) Avoiding adverse drug reactions by pharmacogenetic testing : A systematic review of the economic evidence in the case of TPMT and AZA-induced side effects. *International Journal of Technology Assessment in Health Care* 24(3): 294-302
[84] Compagni A (2008) Avoiding adverse drug reactions by pharmacogenetic testing : A systematic review of the economic evidence in the case of TPMT and AZA-induced side effects. *International Journal of Technology Assessment in Health Care* 24(3): 294-302.
[85] http://www.tpmtassay.com/ accessed 5th December 2008

Nonetheless one lab has recently developed a multiplex genotyping assay for research purposes that includes all 24 currently known functionally relevant alleles for TPMT.[86] This group has undertaken very large clinical studies for research purposes on the pharmacogenetics of TPMT, including a least 20,000 patients over the last seven years. These studies examined the accuracy of genotyping for prediction of different TPMT phenotypes, with a view toward pharmacogenetic applications for thioprine drugs in inflammatory bowel syndromes,[87] identified novel variants of the gene and established multiplex testing methods.[88,89] One kit-maker is developing a panel test for all the known polymorphisms, but other available kits provide fewer mutations.

In the Netherlands a number of laboratories were noted to perform tests for TPMT but the two interviewed reported low interest from clinicians although tests are reimbursed.

The experience of the two UK laboratories interviewed contrasts with the above as clinical interest appears to be much higher. Tests are also lower priced than in other countries.[90] This may be because economies of scale emerge and higher testing volumes also could explain shorter sample reporting times (2-3 days in the UK vs 3-5 days in the Netherlands) discussed at interview.

Recent figures on TPMT test usage by gastroenterologists are available for England and the Netherlands. Fargher et al.[91] surveyed one member of every dermatology, rheumatology, and gastroenterology department in England and obtained a 70% response rate (287 respondents). 67% of responding clinicians reported using a phenotypic TPMT test. More specifically 60% of gastroenterologists used a TPMT test. This compares to only 31% of Dutch gastroenterologists. Interestingly this is considerably higher than the 5% de Boer et al. (2006) reported just two years earlier in a survey to which over 50% of Dutch gastroenterologists responded.[92] In both countries full blood counts are undertaken by almost all clinicians as part of a continuing monitoring. Van Marrewijk et al.[93] note that the majority of Dutch gastroenterologists reported knowledge of TPMT and metabolite monitoring techniques to optimize thiopurine treatment (genotype: 80%; Enzyme: 83% and Metabolite monitoring: 70% of the respondents). However, uptake of these methods in clinical practice is limited: only 31% (n=17) reported using one or more of these techniques sometimes (Genotype/ Enzyme /Metabolite: n=6/7/8), mostly (n=2/0/2), or always (n=1/1/1) (ibid). Fargher et al. did not ask English clinicians to report their knowledge or use of metabolite monitoring.

[86] Schaeffeler E et al (2008) Highly Multiplexed Genotyping of Thiopurine S-Methyltransferase Variants Using MALDI-TOF Mass Spectrometry: Reliable Genotyping in Different Ethnic Groups. *Clinical Chemistry*. 54: 1637-1647.
[87] Schaeffeler E et al (2004) Comprehensive analysis of thiopurine S-methyltransferase phenotype-genotype correlation in a large population of German-Caucasians and identification of novel TPMT variants. *Pharmacogenetics.* 14(7): 407-417.
[88] Schaeffeler E et al (2008) Highly Multiplexed Genotyping of Thiopurine S-Methyltransferase Variants Using MALDI-TOF Mass Spectrometry: Reliable Genotyping in Different Ethnic Groups. *Clinical Chemistry*. 54: 1637-1647.
[89] Schaeffeler E (2006) Three novel thiopurine S-methyltransferase allelic variants (TPMT*20, *21, *22) - association with decreased enzyme function. *Human mutation*. 27(9): 976.
[90] Compagni A et al (2008) Avoiding adverse drug reactions by pharmacogenetic testing : A systematic review of the economic evidence in the case of TPMT and AZA-induced side effects. *International Journal of Technology Assessment in Health Care.* 24(3): 294-302.
[91] Fargher EA et al (2007) Current use of pharmacogenetic testing: a national survey of thiopurine methyltransferase testing prior to azathioprine prescription *Journal of Clinical Pharmacy and Therapeutics.* 32(2):187-95.
[92] De Boer NKH; Mulder CJJ and van Bodegraven AA. (2006) Impracticalities of thiopurine S-methyltransferase determination in daily inflammatory bowel disease practice (Letter to the editor). Alimentary Pharmacology & Therapeutics, 23, 1278.
[93] Van Marrewijk, CJ et al (2008) *Treatment regimes of azathioprine or 6-mercaptopurine in inflammatory bowel disease in clinical practice*, Presentation of the results of a study at the spring meeting of the Dutch Association for Gastroenterology (NVGE), the Dutch Association for Hepatology, the Dutch association for gastrointestinal surgery and the Dutch Association of Stomach-Bowel-Liver Docters (in March 2008. at: www.nvge.nl/uploads/NW/JP/NWJPB-1XFv4FPquaDGnjig/Abstractboek-voorjaar-2008.pdf accessed 17/10/2008.

Dramatic change in test usage has been achieved in English dermatology where usage has increased to 94% where as it was reportedly at zero ten years previously.[94] This appears to be because Dermatologists follow their clinical guidelines more than other surveyed specialties, and the British Association of Dermatologists' guidelines now specifically state TPMT testing should be performed prior to patients starting therapy. In contrast the British Society of Gastroenterology states that they cannot recommend TPMT testing on the basis of many previous years of acceptably safe use of Azathioprine, while the British Society for Rheumatology suggests only that clinicians consider using the test.[95] In the latter speciality only 47% of clinicians use the test. The UK drug information sheet for Azathioprine also does not mention the use of TPMT testing.[96]

In considering the uptake of TPMT testing in England the clinician interviewed suggested that even though Prometheus are yet to promote TPMT testing in Europe, Prometheus's funding of some research, and the enthusing of US clinicians could have given an indirect fillip to the test's use in the UK. While this may have had some impact, it is surprising to see the strongest uptake appears to be in a field that Prometheus has not been actively pursuing, that of Dermatology.

Returning to the issue of lower uptake, de Boer et al. found that Dutch gastroenterologists regarded the continued mandatory use of blood counts, continued cases of neutropenia, and slow time to get TPMT test results back as being reasons explaining the reticence of 64% of respondents to take up the test.

Similar surveys for Germany were not found but considerable variation in clinical guidelines was revealed for use of the same drug by different clinical specialties, as in the UK. TPMT genotyping with Azathiopurine use is discussed in guidelines for autoimmune hepatitis, neurodermitis and myasthenia gravis[97,98,99,100] In the first case, guidelines suggest the need to evaluate the level of activity of the TPMT enzyme before treatment begins. For neurodermitis, more precise indications for dosage are given in cases of low and normal activity measurements of the enzyme. The guideline on myasthenia gravis mentions the possibility to do genotyping as well as phenotypic activity measurement for determining risks of toxicity before treatment with azathiopurine. It also mentions the prevalence of the TPMT gene variant that codes for low activity enzymes. On the other hand guidelines for cerebral vasculitis do not mention the possibility to monitor toxicity when using Azathiopurine.[101]

[94] Fargher EA et al (2007) Current use of pharmacogenetic testing: a national survey of thiopurine methyltransferase testing prior to azathioprine prescription *Journal of Clinical Pharmacy and Therapeutics* 32(2):187-95.
[95] Fargher EA et al (2007) Current use of pharmacogenetic testing: a national survey of thiopurine methyltransferase testing prior to azathioprine prescription *Journal of Clinical Pharmacy and Therapeutics* 32(2):187-95.
[96] http://www.bnf.org/bnf/bnf/current/4781.htm#this
[97] Deutschen Dermatologischen Gesellschaft (DDG); Österreichischen Gesellschaft für Dermatologie und Venerologie; Arbeitskreises Pharmaökonomie in der Dermatologie; Arbeitsgemeinschaft Dermatologische Forschung; Arbeitsgemeinschaft Pädiatrische Dermatologie in der Deutschen Dermatologischen Gesellschaft; Berufsverbandes der Kinder- und Jugendärzte; Arbeitskreises Psycho-Dermatologie; Deutschen Gesellschaft für Allergologie und klinische Immunologie; Gesellschaft für Pädiatrische Allergologie; Berufsverbandes Deutscher Dermatologen; Schweizerischen Gesellschaft für Dermatologie und Venerologie; Schweizerischen Gesellschaft für Allergologie und klinische Immunologie; Arbeitsgemeinschaft Neurodermitis-Schulung; Deutschen Gesellschaft für Kinder- und Jugendmedizin; Arbeitsgemeinschaft Dermatologische Rehabilitation; Deutschen Allergie- und Asthmabundes; Deutschen Kontaktallergie-Gruppe. 2008. *Neurodermitis*. Online at AWMF online: www.awmf.org. Visited 17 October, 2008.
[98] Deutschen Gesellschaft für Neurologie (DGN). 2005. *Myasthenia gravis.* Online at AWMF online: www.awmf.org. Visited 17 October, 2008.
[99] Gesellschaft für Pädiatrische Allergologie und Umweltmedizin (GPA). 2008. *Neurodermitis*. Online: http://www.gpaev.de/typo/fileadmin/user_upload/GPA/dateien_indiziert/Leitlinien/gem_Leitlinie_Neurodermitis.pdf. Visited November 19, 2008.
[100] Gesellschaft für Pädiatrische Gastroenterologie und Ernährung (GPGE). 2007. *Autoimmunhepatitis (AIH)*. Online at AWMF online: www.awmf.org. Visited 17 October, 2008.
[101] Deutschen Gesellschaft für Neurologie (DGN). 2005d. *Zerebrale Vaskulitis*. Online at AWMF online: www.awmf.org. Visited 19 November, 2008.

German guidelines for Crohn's disease do refer to the genetic basis of TPMT activity but advocate use of blood cell counts rather than a pharmacogenetic test.[102] Earlier guidance recommended the genetic test only in exceptional cases.[103] The current guidance for Crohn's is mirrored for other guidelines, such as for treatment of Colitis ulcerosa[104], Myositis Syndrome[105], neuritis[106], and multiple sclerosis.[107]

The above guidance is in contrast to that published in Germany by clinical scientists[108], who advocate both phenotypic and genotypic tests with Azathioprine use. Teml et al., also in Germany, suggest that while weekly determination of the complete blood count in the first month of therapy might be sufficient to avoid side effects, such a measure were heavily dependant on the compliance of patients.[109] They considered it in the interests of patients to screen for TPMT deficiency prior to thiopurine therapy, which would allow exclusion of patients likely to experience neutropenia. Yet the LÖGD (2007) white paper on genetics in public health cites evidence showing that 78% of adverse drug events following azathioprine or 6-mercaptopurine treatment are not related to TPMT genotypic variants.[110] One interviewee suggested current guidelines focused on phenotypic measures, including the blood count, for this reason, as well as because phenotypic tests where less expensive, while another suggested the debate was still ongoing. German authors suggested that reliance on reliance on blood counts is dependent on patient compliance in attending for these tests, which is a draw back.[111]

3.5 The clinical utility and cost-effectiveness of TPMT

In the US, some gastroenterologists view the clinical utility of TPMT testing as being (i) the detection of patients at risk of adverse drug reactions prior to these occurring (ii) earlier arrival at an optimal dose and therefore more rapid benefit for the patient and (iii) in the case of metabolite monitoring, assessment of dosage in a dynamic manner to detect, for example, non-compliance, or mal-absorption.[112] This range of utility is seemingly shared more widely as reflected in the full range of TPMT tests used by Gastroenterologists surveyed by Yip et al.[113] and the willingness of

[102] Hoffman JC et al (2008) S3-Leitlinie "Diagnostik und Therapie des Morbus Crohn". Ergebnissed einer Evideny-basierten Konsensuskonferenz der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten zusammen mit dem Kompetenznetz Chronisch entzündliche Darmerkrankungen. *Zeitschrift für Gastroenterologie*. 46: 1094-1146.
[103] Hoffman J.C and Zeitz M (2003) Chronisch-aktiver Morbus Crohn. *Zeitschrift für Gastroenterologie*. 41: 31-35.
[104] Deutschen Gesellschaft für Verdauungs- und Stoffwechselerkrankungen (DGVS). 2004. *Diagnostik und Therapie der Colitis ulcerosa. Ergebnisse einer "evidenz"-basierten Konsensuskonferenz*. Online at AWMF online: www.awmf.org. Visited 19 November, 2008.
[105] Deutschen Gesellschaft für Neurologie (DGN). 2005c. *Diagnostik und Therapie der Myositiden*. Online at AWMF online: www.awmf.org. Visited 19 November, 2008.
[106] Deutschen Gesellschaft für Neurologie (DGN). 2005e. *Neuritis: Chronische immunvermittelte Polyneuritis, infektiöse Neuritis*. Online at AWMF online: www.awmf.org. Visited 19 November, 2008.
[107] Deutschen Gesellschaft für Neurologie (DGN). 2004. *Diagnostik und Therapie der Multiplen Sklerose*. Online at AWMF online: www.awmf.org. Visited 19 November, 2008.
[108] Deufel D et al (2008) Richtlinie: Labormedizinische Diagnostikl bei der Therapie mit TPMT (Thiopurin-S-Methyltransferase)-abhängigen Pharmaka. *Laboratoriums Medizin.* 28(6): 477-482.
[109] Teml A et al (2007) Thiopurine Treatment in Inflammatory Bowel Disease. Clinical Pharmacology and Implication of Pharmacogenetically Guided Dosing. *Clinical Pharmacokinetics.* 46(3): 187-208.
[110] See van Aken J et al (2003) Prospects and Limits of Pharmacogenetics. The thiopurine Transferase (TPMT) Experience. *American Journal of Pharmacogenomics.* 3: 149-155 – Cited in : LÖGD 2007. *Genetik in Public Health. Teil 1: Grundlagen von Genetik und Public Health. Wissenschaftliche Reihe*. Online at www.loegd.nrw.de, visited November 21, 2008.
[111] Teml A et al (2007) Thiopurine Treatment in Inflammatory Bowel Disease. Clinical Pharmacology and Implication of Pharmacogenetically Guided Dosing. *Clinical Pharmacokinetics.* 46(3): 187-208.
[112] Seidman, E., Dubinsky, M., and Sandborn W. (2006) 'Optimizing thiopurine response in IBD: The clinical utility of TPMT testing and metabolite monitoring' *Gastroenterology and Hepatology* 2 (8) Supplement 6.
[113] Yip JS et al (2008) How are Azathioprine and 6-Mercaptopurine dosed by Gastroenterologists? Results of a survey of clinical Practice Inflamm Bowel Dis 14(4) April. 514-518.

many to use both tests. Indeed economic analysis by Dubinsky et al. (2005)[114] suggests use of a combined TPMT enzyme testing and metabolite monitoring, even at commercial cost, can lead to savings in patient management of around $1300 in the first year of treatment. However, this is based on assumptions that it takes longer to get to maintenance dosages using more incremental dosing (unguided by TPMT testing). In fact, Yip et al.'s (2008) data suggest that US clinicians, especially those treating many patients with Azathioprine, do not take as long to reach maintenance doses as might be assumed. Although it is entirely anecdotal, our one US clinician interviewee stated that they did not see the TPMT test as being sufficiently evidentially supported for him to use it in the treatment of Crohn's disease.

In the EU, interviewees and the scientific literature made fewer references to metabolite monitoring and benefits of using TPMT phenotyping to give higher doses to ultra-metabolizers (as stated by an interviewed EU lab director) are generally not discussed. Instead the literature focuses more on whether or not to use a phenotypic or genotypic test or whether to use a test at all. [115]Although phenotyping and genotyping have been shown to have over 98% concordance[116] there are important limitations for both. Phenotypic tests will give misleading outcomes if patients have had blood transfusions, and genotypic tests can miss individuals with rare mutations (because tests are not generally full sequence based, but screen for selected known mutations). Although US and some laboratories interviewed favoured the phenotypic test, laboratories often used both in varying degrees. In particular two laboratories noted that they used the genotypic test to characterize samples from patients experiencing serious side effects and screened samples with TPMT activity characteristic of polymorphisms. One EU lab reported using the tests in this manner routinely, for which the client is charged only for the phenotypic test.

Although there are at least eight cost-benefit studies for TPMT testing in a range of conditions these have been criticized for using models based on simulations rather than real patient data.[117,118] In particular the utility of testing may be dependent on key variables such as the incidence of fatal adverse drug reactions for which estimates are suggested to be problematic. Nonetheless Compagni et al. concluded that the average cost to a health service per ADR prevented was over 5300€.[119] To address concerns of data inadequacies large scale prospective randomized clinical trials of a thousand patients each have been launched in the UK (in 2006) and the Netherlands (in 2007) funded by the Department of Health and Dutch Medical Research Council, respectively.[120,121] However the UK clinician interviewed suggested it would be difficult to persuade some doctors to join the trial and not to use TPMT tests, given the perceived risk of prescribing Azathioprine without such guidance. No similar cost-effectiveness studies of TPMT testing in were found Germany.

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[114] Dubinsky, M et al (2005) A cost-effectiveness analysis of alternative disease management strategies in patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *American Journal of Gastroenterology* 100: 2239-2247.
[115] Payne K et al (2007) Editorial TPMT testing in rheumatology: any better than routine monitoring? *Rheumatology* 46:727–729
[116] Schaeffeler E et al (2004) Comprehensive analysis of thiopurine S-methyltransferase phenotype-genotype correlation in a large population of German-Caucasians and identification of novel TPMT variants. Pharmacogenetics 14:407–17
[117] Payne K et al (2007) Editorial TPMT testing in rheumatology: any better than routine monitoring? *Rheumatology* 46:727–729
[118] Compagni A.et al (2008) Avoiding adverse drug reactions by pharmacogenetic testing : A systematic review of the economic evidence in the case of TPMT and AZA-induced side effects. *International Journal of Technology Assessment in Health Care* 24(3): 294-302.
[119] Compagni A et al (2008) Avoiding adverse drug reactions by pharmacogenetic testing: a systematic review of the economic evidence in the case of TPMT and AZA-induced side effects. *International Journal of Technology Assessment in Health Care* 24(3): 294-302.

[121] See http://www.zonmw.nl/cgi-bin/search-nl 2.cgi?ul=&ps=10&wf=81&ul=&wm=sub&q=Pharmacogenetic+testing+&t=Projectenpoort, accessed on 17/10/2008

3.6 Lessons on the role of IP in the development and use of genetic tests

The key lessons from this case can be divided into themes relating to the US and EU comparison, the potential for negative impacts of patents on diagnostics, and wider issues related to the translation of genomic research into clinically useful tools.

3.6.1 Lessons from comparing the US and EU

This case provides an example where some key intellectual property (from St. Jude) exist in the USA but not in EU, and where a strong commercial influence has been apparent in the US and not the EU. However it is an imperfect comparison for inferring impacts of DNA patenting in the US or not from patenting in the EU for the following reasons. Firstly there is another DNA patent on specific polymorphisms in the EU that may yet grant (held by Epidauros in Germany). Secondly there is uncertainty around the status of the patents or even lack of awareness of the patents in the EU. Thirdly, laboratories may chose to use the phenotypic test in its place. The recent EPO approval of applications for patents on both the phenotypic and metabolite monitoring methods has further complicated the picture and it is unclear what the impact of these will be at this stage.

In the US, a commercialisation strategy has been pursued to encourage the rapid diffusion of the test. Commercial investment has been supported through patenting and enforcement. It has been necessary for the leading commercialising company to patent or license several technologies to ensure the comprehensive coverage they require to establish a durable franchise. Their high profile sales and marketing of the test is in effect subsidised as sales staff also have other products to discuss with potential client physicians. These efforts appear to have generated an interest in the broad range of TPMT- related applications, although the 'control experiment' of looking at uptake in other fields in the US where Prometheus has not marketed is not studied here. However the extent of current use by US gastroenterologists is also likely to be motivated by clinical guidelines and FDA recommendations to include information about TPMT testing in addition to full blood counts in the drug label, and these obviously are not dependent on Prometheus's sales force for their effectiveness.

The commercialising company has been able to undertake these efforts apparently without licensing the original patent on the wild-type TPMT gene held by the Mayo. It is not clear how many polymorphisms are included in genotypic TPMT test, nor whether Prometheus has licensed these. This seems to illustrate that just because a gene is patented, diagnostics applications are not always covered.

In the EU, it was previously reported there was no major private sector motive driving the adoption of TPMT testing.[122] However it now appears that several companies have invested in TPMT kits. Yet few laboratories appear to be using these products. Clinical uptake has also been mixed. In Germany and the Netherlands TPMT test usage appears to be low, beyond a few large research projects. Yet usage is much higher in the UK, particularly in dermatology where uptake has proceeded rapidly. There is strong evidence to suggest that clinical guidelines are responsible for this. In other fields though, clinical guidelines are less prescriptive and uptake is lower, both in the UK and elsewhere. Intriguingly, gastroenterologists writing guidelines in the EU and US have come to different conclusions on TPMT testing, with the AGA supporting its use and the European Crohn's disease and colitis Organisation not supporting it,[123] although it is not clear why this should be the case.

[122] Hopkins, M et al (2006) 'Putting pharmacogenetics into practice' *Nature Biotechnology* 24(4): 403-410.
[123] Teml A et al (2007) Thiopurine treatment in inflammatory bowel disease: clinical pharmacology and implication of pharmacogenetically guided dosing. *Clinical Pharmacokinetics.* 46(3): 187-208.

3.6.2 Concerns over negative impacts of patents

Caveats from the previous section accepted, it is clear that more than one of the six EU laboratories interviewed had thought about limiting their use of the DNA test because of the perception of a patent being in force, even though this is not the case. EU clinicians however were not aware of this issue or thought that it had not had an impact on test availability.

In the US there is a more clear impact, with Prometheus actively enforcing its property rights. Laboratories either had to send tests to Prometheus for testing, refrain from offering a test, or challenging Prometheus, including through litigation.

This will likely mean that clients are paying a higher fee for tests due to the lack of competition and the presence of enforcement, although it is not clear to what extent this will affect the reimbursement of the test or the level of demand. Another issue is that Prometheus is focusing on sales and marketing for gastroenterologists, as a speciality pharmaceutical company, but may not be attempting to reach other relevant specialties such as rheumatologists or dermatologists (although we have not interviewed these groups so cannot be sure about their usage of the test). If other laboratories are prevented from serving these groups in the meanwhile, then such a strategy could be delaying interventions for patients. This is an impact that could also manifest in the EU, if patents on some TPMT tests are enforced and not others. Even though there are substitute tests, laboratory interviewees and the literature suggests these are best used in combination. An interesting foot note is that the patent on the wildtype gene by Mayo has not prevented the development and enforcement of patents on the gene and this is an important caveat to be noted against arguments of the exceptional nature of gene patents.

There is also a potential impact that may result from operating a centralised testing model rather than outlicensing or selling kits (there are no FDA approved kits for TPMT testing). Prometheus may well be extending the time for some samples to be processed and thereby diminishing the test's utility, as these samples have to be sent on from their laboratory of origin to Prometheus's testing facilities. However it is equally possible that Prometheus's testing process is faster if they have a high-throughout system dedicated to large-scale TPMT testing. This issue has not been investigated here, but it is clear that choice of laboratory and length of reporting times are important concerns for clients. It is also possible that small scale use of TPMT testing by numerous laboratories presents similar issues in the EU, with slower reporting times due to batching of samples for processing (which is efficient with laboratory staff time, but does not benefit patients). Prometheus also suggests that quality may suffer if tests are undertaken at laboratories without expertise with the test, but equally any system with a single service provider is open to criticisms relating to transparency where quality is concerned (for example it is not clear whether Prometheus's test covers the same range of mutations that some EU labs use).

Another concern raised by the US laboratory interviewed is that Prometheus could assert their patent rights in a way that limits research on TPMT testing. This is possible in the US, but less likely in the EU due to the statutory research exemption in most European countries. There is evidence that TPMT does not explain many ADR's related to thiopurines and in the future a range of other genes and their enzymes may be found to play a role in this metabolic process. Prometheus would have a major interest in the development of wider panels of tests. Given that Prometheus seems to have been focused on a single market (Gastroenterology) and geography (the USA) to date and, as they have a relatively small diagnostics business, they contribute only a small faction of the total research field on the application of TPMT. They are therefore a likely beneficiary of continued external research in TPMT and related metabolic fields.

3.6.3 The challenge of translating genomic research into clinical tools and a role for marketing?

The case of TPMT illustrates well the complexities of bringing a diagnostic test into mainstream use. Although the relationship between TPMT deficiency and neutropenia was quickly proved, the extent to which TPMT testing can reduce the incidence of life threatening side effects, or bring other benefits such as more rapid achievement of patient benefit from therapy, has been much more difficult to agree between stakeholders. The cost-effectiveness of TPMT testing is also still the subject of inquiry. In the meanwhile an inestimable amount of research time, effort and money has been invested in TPMT testing and what its role should be a number of clinical fields.

Despite potential negative impacts from patenting, the case demonstrates that other factors also are likely to present more immediate barriers to the use of TPMT testing, including reimbursement arrangements, and perceptions of clinical utility.[124] The evidence above suggests these are particularly an issue in Germany and the Netherlands. Indeed these appear to be the very issues that an active proponent of the test such as Prometheus could address through market-building efforts focused on education of insurers and clinicians. Clearly their task is far from complete in the US and there is clearly further room for more market growth.

Another suggested benefit of patenting is that licensing revenues could be reinvested by academic licensors, who are often not simply spending tax payers money (certainly in the US some are not-for-profit but not necessarily funded by the state), but are reliant on other sources of income to support their ongoing research efforts.

The notion that patents provide a platform for greater investment in sales and marketing, including education, is important to consider in a field where technological adoption is generally accepted to be slow, but equally it is clear there are alternative powerful motivators for adoption such as the development of clinical guidelines.

Other questions are also raised by this. Should the public sector rely on the private sector to accelerate diffusion of novel technologies? What premium should be paid for such an accelerated diffusion process? If another option is preferred by states that do not wish to promote the commercialisation and monopolisation of diagnostic tests, how else is this to be achieved?

The answers to some of these questions undoubtedly lie with answers to questions such as how much faster does the diffusion process proceed and is the intervention worth supporting. Unfortunately, these are questions that often cannot be answered in the early stages of a technology's career. Even more than a decade after the introduction of TPMT testing and despite a host of patents, much investment, and many research studies, there are still ongoing debates into the tests' appropriate usage.

[124] Woelderink, A et al (2006) The current clinical practice of pharmacogenetic testing in Europe: TPMT and HER2 as case studies. *Pharmacogenomics J.* 6: 3–7

Table 7: Patents and patent applications related to diagnostics for Thiopurine S-methyltransferase (TPMT)

Family	Patent	Status (June 2008)	Patent Number	Patent Country	Filing Date	Publication Date	Original owner/ assignees	New owner	Inventors	Title
1	Granted	In force	US 5,470,737*	US	1994-10-03	19951128	Mayo Foundation for Medical Education and Research		Weinshilboum; Richard M. Honchel; Ronald Aksoy; Ibrahim A., Szumlanski; Carol L. Wood; Thomas C. Otterness; Diane M. , Wieben; Eric D.	Stably-transformed cells expressing human thiopurine methyltransferase
2	Filed	PCT - International Search Report Mailed to IB	WO1997007201A1	DE GB NL US	1995-08-14	19970227	ST JUDE CHILDRENS RES HOSPITAL [US]		WILLIAM E [US] ; KRYNETSKI EUGENE Y [US]	Identification of two novel mutant alleles of human thiopurine s-methyltransferase, and diagnostic uses thereof
2	Granted	In force	US5856095A	US	1995-08-14	19990105	ST JUDE CHILDRENS RES HOSPITAL [US]	ST. JUDE CHILDREN'S RESEARCH HOSPITAL, EVANS WILLIAM E [US], KRYNETSKI EUGENE Y [US]	EVANS WILLIAM E [US] ; KRYNETSKI EUGENE Y [US]	Identification of two novel mutant alleles of human thiopurine S-methyltransferase, and diagnostic uses thereof
3	Granted	In force	US6355623*	US	1999-04-08	20010705	HOPITAL SAINTE JUSTINE [US]		SEIDMAN ERNEST G [CA] ; THEORET YVES [CA]	Methods of optimizing drug therapeutic efficacy for treatment of immune-mediated gastrointestinal disorders

3	Granted	In force	EP1115403*	DE, GB, NL	1999-09-24	2005-12-14	HOSPITAL SAINTE JUSTINE [CA]	SEIDMAN ERNEST G [CA] ; THEORET YVES [CA]	Method for optimizing the use of 6-mercaptopurine in the treatment of immune-mediated gastrointestinal disorders
3	Granted	In force	US6680302*	US	2001-12-27	2004-01-20	SEIDMAN ERNEST G; THEORET YVES; HOSPITAL SAINTE-JUSTINE	SEIDMAN ERNEST G [CA]; THEORET YVES [CA]	Methods of optimizing drug therapeutic efficacy for treatment of immune-mediated gastrointestinal disorders
4	Filed	EP1999925207 Withdrawn	WO1999064626A2	DE GB NL US	1999-06-04	19991216	GENOSTIC PHARMA LIMITED ROBERTS, Gareth, Wyn	ROBERTS, Gareth Wyn (GB)	Probes used for genetic profiling
4	Filed	Abandoned -- Failure to Respond to an Office Action	US20030198970A1	US	2002-07-29	20031023	Genostic Pharma Limited	ROBERTS, Gareth Wyn (GB)	Genostics
5	Filed	Abandoned -- Failure to Respond to an Office Action	US20020127714A1	US	2001-02-14	20020912	Variagenics, Inc.	HOUSMAN, David E. (US) LEDLEY, Fred D. (US) STANTON, Vincent P. JR. (US)	Inhibitors of alternative alleles of genes encoding products that mediate cell response to environmental changes
6	Filed	Abandoned -- Failure to Respond to an Office Action	US20070026393A1	US	2001-04-06	20070201	Berlin, Kurt (DE) Piepenbrock, Christian (DE) Olek, Alexander (DE)	Berlin, Kurt (DE) Piepenbrock, Christian (DE) Olek, Alexander (DE)	Detection of variations in the dna methylation profile

6	Filed	Application deemed to be withdrawn	WO0177373A2 *	DE GB NL US	2001-04-06	2001-10-18	EPIGENOMICS AG [DE]; BERLIN KURT [DE]; PIEPENBROCK CHRISTIAN [DE]; OLEK ALEXANDER [DE]		Berlin, Kurt (DE) Piepenbrock, Christian (DE) Olek, Alexander (DE)	Detection of variations in the dna methylation profile
6	Filed	Application is deemed to be withdrawn, reason: reply to examination report not received in time	EP1278892*	DE GB NL	2001-04-06	2003-01-29	EPIGENOMICS AG [DE]		BERLIN KURT [DE]; PIEPENBROCK CHRISTIAN [DE]; OLEK ALEXANDER [DE]	DETECTION OF VARIATIONS IN THE DNA METHYLATION PROFILE
6	Filed	Abandoned -- Failure to Respond to an Office Action	US2007026393 *	US	2001-04-06	2007-02-01			BERLIN KURT [DE]; PIEPENBROCK CHRISTIAN [DE]; OLEK ALEXANDER [DE]	Detection of variations in the dna methylation profile
6	Filed	EP2001940158 ; EP1278892; US Application Abandoned -- Failure to Respond to an Office Action	WO2001077373A2	DE GB NL US	2001-04-06	20011018	Epigenomics AG (DE)		Berlin, Kurt (DE) Piepenbrock, Christian (DE) Olek, Alexander (DE)	Detection of variations in the dna methylation profile
7	Granted	In force	US6610489B2	US	2001-04-27	20030826	WOLFFE ALAN ; URNOV FYODOR (+5)	SANGAMO BIOSCIENCES, INC.	WOLFFE ALAN [US] ; URNOV FYODOR [US]	Pharmacogenomics and identification of drug targets by reconstruction of signal transduction pathways based on sequences of accessible regions

8	Granted	In force GB: Paid national fees	US6576438B2	US	2001-05-16	20030610	BARSTAD PAUL; PROMETHEUS LABORATORIES, INC.	BANK OF AMERICA, N.A.	BARSTAD PAUL [US]	Method of determining thiopurine methyltransferase activity
8	Granted	De and NL: LAPSED FAILURE TO SUBMIT TRANSLATION OF THE DESCRIPTION OR TO PAY THE FEE WITHIN THE PRESCRIBED TIME-LIMIT	EP1285085B1	DE GB NL	2001-05-16	20080116	PROMETHEUS LAB INC [US]		BARSTAD PAUL [US]	Method of determining thiopurine methyltransferase activity
8	Granted	In force	US7138250B2	US	2003-05-02	20061121	BARSTAD PAUL ; PROMETHEUS LABORATORIES, INC	BANK OF AMERICA, N.A.	BARSTAD PAUL [US]	Method of determining thiopurine methyltransferase activity
9	Filed	Abandoned -- Failure to Respond to an Office Action	US20030017459A1	US	2001-06-26	20030123	Ramanathan, Murali (US)		RAMANATHAN, Murali (US)	Method for predicting drug clearance and individualized dosage
9	Filed	PCT - International Search Report Mailed to IB	WO2002000935A1	DE GB NL US	2001-06-26	20020103	The Research Foundation Of State University Of New York (US)		RAMANATHAN, Murali (US)	Method for predicting drug clearance and individualized dosage

			US http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearch-bool.html&r=1&f=G&l=50&co1=AND&d=PTXT&s1=6,946,258.PN.&OS=PN/6,946,258&RS=PN/6,946,258 - h0#h0http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearch-bool.html&r=1&f=G&l=50&co1=AND&d=PTXT&s1=6,946,258.PN.&OS=PN/6,946,258&RS=PN/6,946,258 - h2#h26946258*							
10	Granted	In force		US	2002-03-04	20050920	Biologix Diagnostics, LLC [US]		Padhye; Nisha V., Quintanar; Andre', Nelson; R. Michael	Rapid, immunochemical process for measuring thiopurine methyltransferase

11	Filed	Abandoned -- Failure to Respond to an Office Action	US2006078879 *	US	2003-02-04	2006-04-13	EPIDAUROS BIOTECHNOLOGIE AG	SCHWAB MATTHIAS [DE]; SCHAEFFELER ELKE [DE]	Polymorphisms in the human gene for tpmt and their use in diagnostic and therapeutic applications
11	Filed	Examination is in progress	WO03066892*	DE, GB, NL, US	2003-02-04	2003-08-14	EPIDAUROS BIOTECHNOLOGIE AG [DE]; SCHWAB MATTHIAS [DE] (+1)	SCHWAB MATTHIAS [DE]; SCHAEFFELER ELKE [DE]	POLYMORPHISMS IN THE HUMAN GENE FOR TPMT AND THEIR USE IN DIAGNOSTIC AND THERAPEUTIC APPLICATIONS
12	Filed	Response to Non-Final Office Action Entered and Forwarded to Examiner	US20040048279A1	US	2003-05-14	20040311	Olek, Alexander (DE) Piepenbrock, Christian (DE) Berlin, Kurt,(DE)	OLEK, Alexander (DE) PIEPENBROCK, Christian (DE) BERLIN, Kurt (DE)	Method for detecting methylation states for a toxicological diagnostic
13	Filed	PCT App. Not Ent. Europ. Phase	WO2004033722A2	DE GB NL US	2003-09-23	20040422	SCIONA LTD [GB] ; ROBERTS GARETH WYN [GB] (+1)	ROBERTS GARETH WYN [GB] ; GRIMALDI KEITH [GB]	Genetic profiling and healthcare management: adme (absorption, distribution, metabolism & elimination) & toxicology patent application
14	Filed	Non Final Action Mailed	US20050100926A1	US	2003-11-10	20050512	Chen, Yuan-Tsong [TW], Hung, Shuen-lu [TW], Chung, Wen-Hung [TW], Wu, Jer-Yuarn [TW]	Chen, Yuan-Tsong [TW], Hung, Shuen-lu [TW], Chung, Wen-Hung [TW], Wu, Jer-Yuarn [TW]	Risk assessment for adverse drug reactions

14	Filed	Application Undergoing Preexam Processing	WO2005047544A1	DE GB NL US	2004-06-18	20050526	ACADEMIA SINICA [TW] ; CHEN YUAN-TSONG [TW] (+3)		CHEN YUAN-TSONG [TW] ; HUNG SHUEN-IU [TW] (+2)	Risk assessment for adverse drug reactions
15	Filed	PCT App. Not Ent. Europ. Phase	WO2005038049A2	DE GB NL US	2004-10-06	20050428	HEINRICH GUENTHER [DE] ; ROOTS IVAR [DE]		HEINRICH GUENTHER [DE] ; ROOTS IVAR [DE]	System and method for optimizing drug therapy
16	Filed	Response to Non-Final Office Action Entered and Forwarded to Examiner	US20070009897A1	US	2004-11-04	20070111	Sankyo Company, Limited [JP]		KOIZUMI, Makoto [JP], Kawasaki-shi, Kanagawa [JP]	Method of detecting genetic polymorphism
17	Filed	Non-Entry Into The National Phase In: DE	WO2005066362A2 and A3	DE GB NL US	2005-01-07	20050721	BAYER HEALTHCARE LLC [US] ; STROPP UDO [DE]		STROPP UDO [DE]	Haplotypes and polymorphisms linked to human thiopurine s-methyltransferase deficiencies
17	Filed	Published in EPO (New Applicant: Siemens)	EP2005700724	DE GB NL	2005-01-07	20061004	BAYER HEALTHCARE LLC [US]	SIEMENS HEALTHCARE DIAGNOSTICS INC.	STROPP UDO [DE]	Haplotypes and polymorphisms linked to human thiopurine s-methyltransferase deficiencies
18	Filed	Notice of Appeal Filed	US20060292695A1	US	2005-09-22	20061228	Roslin Institute, [GB] CXR Biosciences Ltd., [GB]		CLARK, A. John [GB], CLARK, Helen [GB], WOLF, C. Roland [GB],	Methods and kits for drug screening and toxicity testing using promoter-reporter cells derived from embryonic stem cells
18	Filed	Application Undergoing Preexam Processing	WO2007002568A1	DE GB NL US	2006-06-22	20070104	GERON CORP [US]; CLARK HELEN [GB] (+1)		WOLF C ROLAND [GB]; CLARK A JOHN	Reporter hepatocytes and other cells for drug screening and toxicity testing

19	Filed	Application Dispatched from Preexam, Not Yet Docketed	US20080152632A1	US	2006-06-22	20080626	Roslin Institute (GB)|CXR Biosciences Ltd. (GB)		CLARK, A. John (US) CLARK, Helen (GB) WOLF, C. Roland (GB)	Promoter-reporter cells for determining drug metabolism, drug interactions, and the effects of allotype variation

N.B.
* Patents in this table have been found by use of a key word search of patent databases, except for those numbers with an *. The latter have been found through discussion with interviewees and/or published sources. Their status was current in November 2008.

IV. HPV

4.1 Introduction

Whilst the policy debate about gene patents has focused primarily on applications in clinical genetics, in particular the BRCA test, this is not the only area of molecular diagnostics to be affected by the growth in biomarker IP. The field of infectious diseases has been affected by patents as well (see WP2), in relation to Hepatitis C Virus, Human Immunodeficiency Virus and Human Pappiloma Virus (HPV) The infectious disease market has been central to the growth of the molecular diagnostics sector. The first FDA clearance for a clinical diagnostic based on nucleic acid probe technology was granted to Gen-Probe Inc. in 1985, and in the course of the next five years most of the other nucleic acid–based tests kits commercialised were in the field of infectious diseases.[125] Infectious disease testing is commonly accepted to have been the biggest growth area for molecular diagnostics in the last ten years and one where there remains significant potential, particularly in terms of test volume. In general the infectious disease market is one where patents have been exploited by companies producing kits rather than companies producing LDTs, probably as a consequence of market size. HPV testing for cervical cancer is very commercially attractive, since even as an adjunct to a cytology test there is still a large market but if HPV is used in conjunction with cytology testing or to replace it, then the potential is huge.

4.2 Biological background

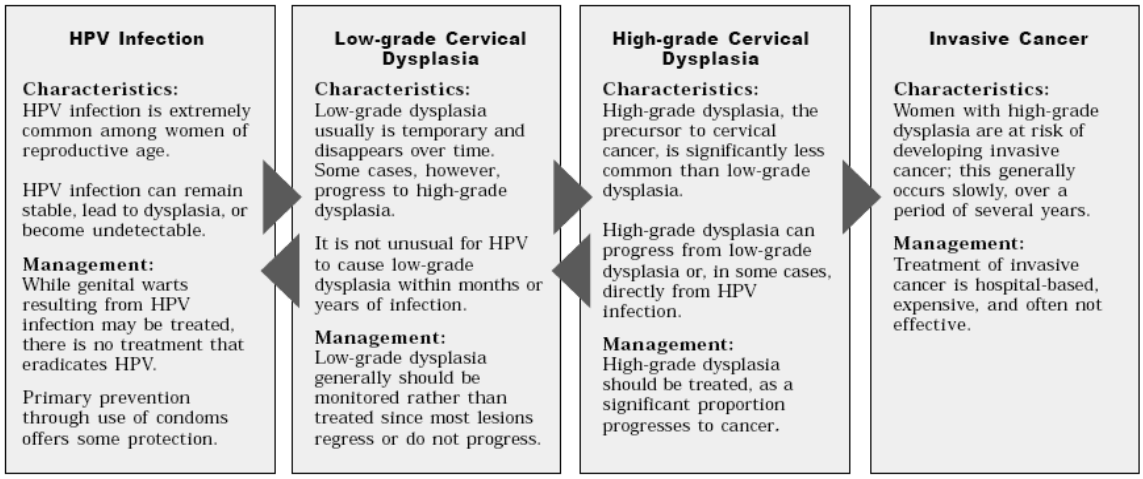
The role of HPV in cervical cancer was established with the discovery of tumorigenic virus type HPV 16 in 1983 by a team led by Professor Harald zur Hausen at the German Cancer Research Center, in Heidelberg (a discovery for which he subsequently received a Nobel Prize). Since then there has been significant progress in understanding of cervical carcinogenesis and it is now generally accepted that HPV is an essential factor in the causation of the disease. Genital human papillomavirus (HPV) is a common virus which is passed on through genital contact. It is the primary cause of both cervical disease leading to cancer and actual cervical cancer. The majority of sexually active men and women will acquire HPV at some time in their lives, but in most cases they will not become aware of the virus. There are over 100 subtypes of HPV and most are harmless, usually causing no signs or symptoms. However, while most HPV clears up within two years, if infection is persistent, it can lead to integration into the cellular genome causing inactivation of tumour suppresser genes, suppression of apoptosis, genetic instability and the development of precancerous change. This process is associated with a small number of high-risk HPV strains (such as HPV-16, HPV-18, HPV-31, and HPV-45) and if left untreated, can eventually lead to cervical cancer[126] (to a lesser degree these HPV types are also associated with cancers of the vagina, vulvae, penis and anus). However, presence of high-risk HPV strains does not always lead to cancer - women younger than age 30 have a high rate of infection with high-risk HPV (15–46 percent), and most infections will be transient.[127]

Early stage cervical cancer is characterized by pre-cancerous cells called cervical intraepithelial neoplasia (CIN), and these are divided into “grades” of severity, graded CIN1+, CIN 2+ and CIN3+. Typically, cervical cancer is a slow-progressing disease and if the disease is

[125] Schifreen, R (2000) Molecular diagnostics: The challenge for the future. *IVD Technology Magazine* November/December
[126] Centers for Disease Control (2007) *What Women Should Know Before They Get a Pap and HPV Test* Accessed onlne at : http://www.cdc.gov/std/hpv/common-clinicians/InsertPap.pdf
[127] Goldie SJ; Kim JJ and Myers E (2006) Cost-effectiveness of cervical cancer screening. *Vaccine* 24S3, S3/164–S3/170.

caught early on whilst still at the cellular dysplasia phase then progression to cervical cancer can be prevented.

Figure 2 Natural history of cervical cancer and implications for clinical management[128]



Cervical carcinoma is the second most common form of cancer in women, and the third leading cause of cancer death in women worldwide. An estimated 555,100 new cases will occur in the world during 2007 and an estimated 309,800 deaths are expected to occur in 2007. Since the 1960s both incidence and mortality rates have dropped in many developed countries due to the introduction of screening and intervention programmes. Invasive cervical cancer is one of the most successfully treated cancers. The relative five-year survival rate for cervical cancer patients diagnosed at localized stage in the United States is 92%.[129] Treatment options for pre-invasive lesions are electrocoagulation (the destruction of tissue through intense heat by electric current), cryotherapy (the destruction of cells by extreme cold), laser ablation, or local surgery. Invasive cervical cancers generally are treated by surgery, radiation, or both, as well as chemotherapy in some cases.

The initial discovery of HPV 16 in 1983 by by Professor Harald zur Hausen and colleagues was followed in 1984 by the same team cloning HPV 16 and HPV 18 from patients with cervical cancer. Further research was facilitated by the team's decision to make these clones freely available to the global scientific community. However, HPV has subsequently become the subject of considerable patenting activity by academic researchers, diagnostic companies and pharmaceutical firms.

4.3 HPV patents and key assignee exploitation strategies

Of our three case studies HPV is the one where the highest volume of patenting activity has occurred, leading to what may be fairly termed a patent thicket due to the number of patents and their potential overlaps. This has given rise to significant IP litigation in the United States, primarily between rival diagnostic companies. Our research revealed 74 patent families held in Europe and the US by both public sector institutions and life sciences companies. The breadth of patents in part stems from the variety of HPV strains which can each be subject of separate patents, but also from the different types of patent which might be granted. There are three main forms of patents relating to HPV tests:

- Entire genome sequence for a strain of HPV
- Probes that find some or all of the strains
- Means of identifying a strain of HPV using a specific platform

[128] This figure is drawn from Malloy, C et al (2000) *HPV DNA Testing: Technical and Programmatic Issues for Cervical Cancer Prevention in Low-Resource Settings* (PATH)
[129] American Cancer Society (2007) *Global Cancer Facts and Figures 2007* (Atlanta, GA: ACS)

4.3.1 Key assignees and key claims for granted patents

HPV patenting began when the US company Life Technologies was granted three US patents in 1989 and one in 1990 on HPV types 35, 44, 43 and 56 respectively. A single patent containing related claims to the above was granted in Europe. These patents were re-assigned to another US biotech company, Digene, when they acquired Life Technologies (these patents have now reached the end of their full terms and have expired). In addition, Digene was granted the US patent No. 5,116,734 in 1992 on a kit and a method for detecting peroxidase bound to HPV nucleotides. This family also contains an application abandoned in Europe. Additionally, Digene was granted an EPO and a US patent in 2000 and 2001 on a non-radioactive hybridization assay (hybrid capture) and kit for detecting HPV and other infectious agents. This is the technology which Digene uses in their commercial kits.

Many of the most important HPV patents have been granted to academic research institutions: Georgetown University in the United States and the Institut Pasteur in France. Georgetown University was granted a US patent on the L1 gene sequence and its uses for detecting various types of HPV in 1991, and a patent in this family was granted by the EPO in 1992. The latter is now more than 20 years old and has expired. Georgetown University was also granted an EPO and US patent on HPV DNA or RNA for HPV type 52 and methods in 1994 and 1997 respectively. The Institut Pasteur had a series of patents related to three patent families granted from 1994 onwards in the US (6 patents) and Europe (4 patents). on the DNA sequences of HPV types 2d, 5,6, 10, 28, 29, 31, 32, 39, 49, 50, 54, and 55, and fragments of HPV genes E1, E6-E7, L 1 and L2. These patents were re-assigned to Roche Molecular Systems and Hoffmann La Roche (CH). Two of the European patents have now expired due to their filing dates being in 1985 and 1987.

Moreover, other assignees can be found in this field:

- Hoffmann La Roche Inc. (a US subsidiary of Hoffmann La Roche AG) and the University of Rochester (US) were granted the US patent No. 5,283,171 in 1994 (currently expired) and US patent No. 5,447,839. Cetus Corp. (a US company) originally was granted an EPO patent in 1996 covering on detection of a wide number of HPV types by specified probes (namely on types 5, 6, 8, 11, 16, 18, 26, 27, 30, 31, 33, 35, 39, 40, 41, 42, 43, 45, 47, 48, 51, 52, 53, 54, 55, 57, 58, and 59) and possibly others using consensus probes by polymerase chain reaction (PCR). This patent was re-assigned to Hoffmann La Roche AG (Switzerland). In 1997 and 1998, Roche Molecular Systems (a US company of the conglomerate Roche) was granted two US patents, which were re-assigned to Hoffmann La Roche Inc.
- Stichting Researchfonds Pathologie (a Dutch foundation) was granted a US and EPO patent in 1994 and 1996 on primers and process for detecting unspecified HPV genotypes by PCR.
- BioMerieux (a French company) was granted an EPO patent in 1996 on a method for detecting a nucleotide sequences from HPV types 6,11, 16 and 18 by sandwich hybridization.
- Abbott Laboratories (a US company) was granted an EPO and a US patent in 1998 and 1999 on the use of conserved oligonucleotide primers to amplify DNA sequences from unspecified HPV types DNA sequences.
- Polartechnics (an Australian company) was granted two US patents on a method of detection of carcinogenic HPV types 16, 18 and 33 and low risk HPV types 6 and 11 HPV in 1998 and 2001.
- Gene Pool (a US company) was granted a US patent in 1999 on a method for sequence-specific detection of nucleic acid hybrids using a DNA-binding molecule or assembly capable of discriminating perfect hybrids from non-perfect hybrids. The example given was a molecule that binds to unspecified HPV types. The Gene Pool filed an EPO application in 2007. In this patent family, one US application was abandoned (due to failure to respond to an office action) but Gene Pool filed an EPO application in 2007.
- Columbia University (US) was granted a US patent in 1999 on detection of high oncogenic-risk HPV types 16, 18, 31, 33, 35, 39, 45, 56, 58 and 65 in high-grade cervical lesions and cancers by a PCR/ELISA assay. The PCT application filed in 1996 is still pending and so GB, NL and DE patents have not yet been granted (if indeed this application has not been abandoned).

- Merck and Co. Inc. (a US company) was granted a US patent in 2005 and two EPO patents in 2006 (similar US patent abandoned) covering nucleotide probes and method for detecting HPV6, HPV11, HPV16 and HPV18.
- Bayer HealthCare LLC (a German company) was granted an EPO patent in 2006 on a method, reagent and kit for genotyping of unspecified HPV types and HPV51.
- GenoID (a Hungarian company) was granted an EPO and a US patent in 2006 and 2007 on amplification-hybridisation method for detecting and typing HPV types 3, 4, 6, 7, 9, 10, 11, 12 13, 14, 16, 18, 20, 24, 26, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 39, 40, 41, 42, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59, 60, 61, 66, 67, 68, 72, 74 and 77.
- Norchip (a Norwegian company) was granted an EPO patent in 2007 on method for detecting HPV mRNA for HPV types 16, 18, 31, 33 and 45. Norchip filed a PCT application in 2003 which was withdrawn in EPO in 2006 and one US abandoned in the US (because of failure to respond to an office action) and one still in prosecution. In this patent family, there were two US applications (one was abandoned). Norchip filed also an EPO application in 2006 (still pending) and a US application in 2007 (still pending).
- Gen-Probe (a US company) was granted a US patent in 2008 on detection of nucleic acids from m multiple types of HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. Gen-Probe filed a PCT application in 2006.
- Hybridon (a US company) was granted an EPO patent in 2000 and a US patent in 2003 for a method of detection of HPV using oligonucleotides to hybridise to nucleic acid sequences from types 1, 19, 30, 31, 32, 33, 38, 50, 52, 53, and 56
- Quantovir AB (a Swedish) company was granted a US patent in 2001 for predicting progression to cancer on the basis of viral load for HPV 16, 18 and 30-60.
- The Institut Curie (France) was granted a US patent in 2007 on a method of predicting relapse of cancer patients with HPV types 16 and 18.
- The Penn State Research Foundation (US) was granted two US patents in 2003 (the PCT application is still pending) and 2007 on further applications of HPV testing (e.g. cervical dysplasia).
- Sung-Wook Yoon, Tae-Shin Park, Jeong-Mi Kim and Mi-Sun Park (South Korea) were granted a US patent in 2007 for genotyping HPV.
- Marc Ramael (Belgium) was granted an EPO patent in 2008 for a method and kit to detect the presence of HPV 16, HPV18, HPV 31, HPV 33, HPV 35, HPV 52 and HPV 58.

Our research revealed other assignees with patents mentioning HPV but whose patents are not listed here as they are deemed irrelevant to diagnostics in this field. Apart from the present patent assignees who have also filed applications, 49 relevant patent families have been filed either in the USPTO, EPO or WIPO by a variety of applicants, including companies, academic institutions and public agencies. Among the patent applications, many of these are 38 applications still pending, which mainly protect methods. However, there exist nine patent applications which have been abandoned, seventeen withdrawn and one that was abandoned without entering into the European phase. Apart from that, one patent application has been rejected with no subsequent action, and another one has been appealed.

4.3.2 Exploitation strategies

One company dominates the HPV testing market: the US biotech Digene (established in 1985 and acquired by Qiagen in 2007). Crucial to Digene's near-monopoly position has been the successful exploitation of HPV patents (both its own and those it has licensed in on an exclusive basis). The value of Digene's IP is indicated by the fact that the company was acquired by Qiagen in 2007 for $1.6 billion. Qiagen's press release announcing the deal made reference to Digene's "leading IP positions in HPV".[130] We will consider Digene's success by analysing its exploitation strategies through licensing/acquiring and enforcing its IP; its research and development activities; and its promotional efforts to build a market.

4.3.2.1 Licensing/acquisition of key IP

[130] QIAGEN and Digene Announce Merger 3 June 2007
http://www1.qiagen.com/about/pressreleases/PressReleaseView.aspx?PressReleaseID=21

Aside from Digene's own IP the key patents in the HPV thicket are those which were first granted between 1989 and 1997 to three organisations: the US company Life Technology, the Institut Pasteur and Georgetown University. Digene acquired Life Technology in 1990 gaining both its biomarker IP and the Hybrid Capture methodology platform. Digene also acquired licenses for the Georgetown and the Institut Pasteur patents.

Georgetown University granted Digene an exclusive worldwide license to its HPV patents (it is interesting to note that according to the company's 1999 annual Dr Attila Lorincz, Vice President, Research and Development and Scientific Director and one of the founders of the company was an Adjunct Associate Professor in the Georgetown University Medical School Department of Pathology). Details of the initial agreement are not known but in 2004 Georgetown sued Digene alleging breaches of the royalty agreement and claiming it was entitled to 8% of product sales. The dispute was settled in 2005. Under the settlement, Digene made a payment of $7.5 to Georgetown and will make royalty payments of 5-6% of future product sales to the university until July 1, 2014, for one patent, and Oct. 15, 2008, for the second patent.[131]

In 1990 Institut Pasteur granted a license to Life Technologies for U.S. Patent No. 4,849,331 titled Human Papillomavirus 44 Nucleic Acid Hybridization Probes and methods for Employing the Same and U.S. Patent No. 4,849,332 for HPV 35 (again for probes and related methods). Institut Pasteur also granted a license to Beckman Coulter. In 2000 Institute Pasteur and Inserm granted Digene an exclusive worldwide license to its US patents for HPV68 and HPV70.[132] However, Digene's position in relation to these patents was somewhat weaked in 2002 when Roche acquired the entire HPV intellectual property estate of Institut Pasteur, including cross license agreements such as those between Digene and Institut Pasteur.[133]

4.3.2.2 Enforcement of IP

Digene's dominant patent position has been vigorously defended in the United States, where there has been a series of suits relating to HPV patents. The earliest HPV patent litigation would appear to be a suit brought by Life Technologies in December 1996, when they sued a US competitor called Clontech Laboratories, Inc. for infringement of U.S. Patents Nos. 5,244,797 and 5,668,005.[134] Having acquired Life Technologies in 1990, Digene would appear to have inherited their willingness to litigate but have themselves been the subject of litigation.

Chronology of Digene's patent litigation
2001 Digene sues Ventana (and subsequently Beckman Coulter)
2002 Enzo Biochem sues Digene
2004 Georgetown University sues Digene
2005 Third Wave sues Digene
2006 Digene files against Roche (Gen-Probe joint the suit)
2007 Digene suesThird Wave

In 2001 Digene filed a suit against Ventana, claiming that their Inform test infringed Digene's IP on HPV types 35 and 44. This litigation became further complicated in 2002 when Ventana acquired Beckman Coulter's HPV business including a 1991 sub-license with Institut Pasteur for HPV IP. This development led Digene to add Beckman as a co-defendant to its action, claiming that the company had no right to assign its HPV business and intellectual property to Ventana because the 1990 Cross-License Agreement with Institute Pasteur prohibited such a

[131] Adler, N (2005) Digene, Georgetown University settle legal dispute *Washington Business Journal* July 14 http://washington.bizjournals.com/washington/stories/2005/07/11/daily34.html
[132] Digene. Digene exclusively licenses HPV-68 patent. Digene press release 26 April 2000
[133] PR Newswire. Digene Announces Assignment by Institut Pasteur of Cross License. Accessed online at http://www.ipfrontline.com/printtemplate.asp?id=593
[134] United States Court Of Appeals For The Federal Circuit (2000) *99-1550 Life Technologies, Inc., V. Clontech Laboratories, Inc.* September

sale. In July 2006 the International Center for Dispute Resolution arbitration panel ruled on the Beckman suit and both parties have subsequently claimed victory. Beckman state that their assignment of their Institut Pasteur licenses to Ventana has been judged lawful, whilst Qiagen state that the panel upheld their "contractual rights relating to various HPV materials and intellectual property" and ruled Beckman's "attempted assignment of certain HPV patent rights to Ventana was impermissible."[135] Digene's initial suit against Ventana was settled in December 2007. As part of that settlement an undisclosed cash consideration was paid by Ventana to Qiagen who acknowledged that Ventana had a lawful right to IP gained through its purchase of Beckman. Ventana continue to sell HPV ASRs, however the company was acquired by Roche in 2008, who have their own HPV tests which have been filed for FDA approval.[136]

In December 2006 Digene filed with the International Centre for Dispute Resolution for binding arbitration against Roche for breaching its license agreement by entering into an alleged Supply and Purchase agreement with Gen Probe. In 2005 Roche had agreed to sell DNA probes to Gen Probe for use in its Aptima HPV test. Digene's suit echoes its dispute with Beckman in alleging that Roche are sub-licensing products to Gen Probe. In April 2009 Gen-Probe issued a press release stating that the ICDR panel had "issued an interim award that dismisses with prejudice all of Qiagen's claims."[137] Roche are seeking FDA approval for two HPV tests, both of which are available in Europe. Meanwhile Gen-Probe launched its HPV test in Europe in May 2008 two months after starting a clinical study in the US which will provide data for the company to file for FDA approval some time in 2009.[138]

In 2002 Digene was itself subject of a patent-infringement suit brought by Enzo Biochem over a method for detecting infectious viruses. In 2004 Digene settled the for $16 million, plus guaranteed royalty payments in future years.[139]

In October 2005 Digene, was again the subject of litigation in this case by Third Wave, a US company developing a range of molecular diagnostics, including HPV ASRs. Although Third Wave initiated the suit, they claimed that they had done so only in response to threats of litigation from Digene. Third Wave contended that Digene has "alleged through its counsel that Third Wave's products infringe Digene's [four] patents," and asked the court for a declaration that the company has not infringed any of the four patents, and that the patents are invalid.[140] A temporary halt to hostilities resulted was achieved in January 2006 when both companies agreed not to sue each other for a year. A year late Digene sued Third Wave demanding that the company was infringing Digene's US patent 5,643,715 (the Georgetown patent on HPV strain 52). In March 2007 Third Wave countersued alleging that Digene has "abused its monopoly power to thwart competition", and as a consequence, Third Wave stated they had thus far gained less than 2 percent of the US HPV diagnostics market. Third Wave was acquired by Hologic in 2008. Hologic are a medical imaging and diagnostics firm who also own Cytc the company which produce the ThinPrep test which is the leading liquid based cytology test for cervical cancer and whose technology allows labs to collect samples which can also be used for HPV testing (Cytc had attempted to acquire Digene in 2002 but the move was blocked by the US government).

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[135] Beckman Coulter. Beckman Coulter Announces Results on Arbitration With Digene Regarding 2002 Sale of Certain Assets to Ventana. Press release July 2006 http://phx.corporate-ir.net/phoenix.zhtml?c=64256&p=irol-newsArticle&ID=889775&highlight= and Qiagen Financial Report 2007 http://www1.qiagen.com/about/InvestorRelation/aboupdf/AR2007.pdf p58

[136] Orenstein, B. (2008) Roche finally acquires Ventana. *IVD Technology* April http://www.devicelink.com/ivdt/archive/08/04/002.html

[137] Gen-Probe. Gen-Probe, Roche Prevail in Arbitration With Digene Concerning Human Papillomavirus Agreement-Press release 1 April 2009 http://www.gen-probe.com/news/PressReleaseText.asp?releaseID=1272322

[138] Gen-Probe. 2008 Annual Report p.5

[139] Digene settles patent lawsuit for $30.5 million *Baltimore Business Journal* October 15, 2004

[140] Facing thorny HPV/HCV patent landscape, Third Wave decides the best defense is a good offense *GenomeWeb* 20 October 2005

Commenting on the Third Wave/Digene litigation industry analyst Bruce Cranna said: "Digene believes it has solid intellectual property rights concerning HPV subtypes 52, 58, and 68, but most in the industry believe the other 10 strains are pretty much in the public domain or will be shortly." Third Wave CEO Kevin Conroy argued that: "Digene is not the exclusive owner of the right to detect HPV subtype 52".[141] On April 1 2009 the US Court of Appeals for the Federal Circuit rejected both Third Wave's anti-trust suit and Qiagen's claim for patent infringement seemingly confirming Third Wave's view that Digene's patent was sufficiently narrow to be worked around.[142] The ruling came shortly after Hologic had gained FDA approval for its two HPV tests (Third Wave's HPV test was CE-marked for use in Europe in December 2007 and is available through a series of European distributors). [143]

It would appear that aside from Gen-Probe/Roche pursuing legal costs, there is now no outstanding HPV patent litigation between Qiagen/Digene and any other party. Whether the company becomes less litigious in the light of the ruling on its HPV 52 patent and the expiration of some its other key patents remains to be seen. From a European perspective the most striking aspect of this complex web of litigation is that it has taken place solely in the United States. There is no evidence that Digene have brought legal action against any of the companies who are currently solely focused on the European market, such as Innogenetics, NorChip and mtm Laboratories.

Amongst our German interviewees one clinician mentioned not being aware of any patent on HPV genes and thinking that current IPR could only consist of methods patent (EU CLINICIAN). This person approved patents on methods as a spur for further developments but not on genes, where it would be seen to hamper progress. Other respondents however were aware of Digene's patents on HPV sequences (EU LAB1; EU LAB2). Our UK interviewee was not aware of problems arising from Digene's patents and thought that the number of companies developing rival tests indicated how competitive the field was becoming. (EU clinician2). A German respondent also took the view that competition was growing, as he had witnessed the development of a number of new assays from various companies but that companies needed to assess the current patent positions and potential licensing agreements before moving to commercialisation.(EU LAB2). This interviewee expressed the view that companies "talk to one another" and solve problems between themselves, and that these conflicts do not affect patient and indeed laboratory access to test kits (EU LAB2). However, a German research laboratory offering testing as a service mentioned that HPV sequence patents had hindered the development of alternative HPV tests. Laboratories and a clinician were not able to comment on this issue further than to say that in general they understand that patents play a role in providing industry with the proper rewards for their development work (EU LAB1; EU LAB2; EU CLINICIAN1).

Digene's failure to litigate in Europe is not the only apparent indication of a targeted approach to enforcement; its US litigation has all been against other kit makers despite the fact that, as stated in its 2003 annual report, the company has been aware of the use of LDTs by some US labs:

> We are also aware that a significant number of laboratory organizations and other companies are developing and using internally developed, or "home-brew," human papillomavirus tests. We are monitoring these activities.[144]

However, one US interviewee had developed their own LDT for HPV genotyping and stated that they had made this decision reluctantly because of anxiety about the possibility of being sued for patent infringment "we did it, but they could come after us". However, they also felt that Digene were unlikely to target smaller labs: "We're small fish, they're not going to go after

[141] The Emmes Group (2007) *Diagnostic Testing & Healthcare Industry News Update* May 21 http://dxma.org/UserFiles/NewsUpdates/may21emmesupdate.pdf
[142] GenomeWeb. Court of Appeals Sides with Qiagen in HPV Antitrust Case. April 01, 2009 http://www.genomeweb.com/print/914217?page=show
[143] Hologic. FDA approves two Hologic HPV tests. Hologic press release. http://www.hologic.com/ir/nr031309.htm
[144] Digene. 2003 Annual Report, accessed online at: http://www.getfilings.com/o0000950133-03-003226.html

us." and neither were they aware of patent enforcement against the major commercial lab who had also developed its own genotyping LDT (US Lab 1).

4.3.2.3 Building the clinical evidence base

Whilst we shall focus our discussion on Digene's R&D activity, it should be noted that they were not the only company helping to build the evidence base for the clinical relevance of HPV. Roche's linear array HPV test was provided free to researchers in the 1990s and one interviewee stated that it had a major impact by helping to identify which strains of HPV are associated with cancer (US kit maker). Nevertheless, given the apparent strength of Digene's patent position and their virtual monopoly on the US market since they launched their test nine years ago, HPV would appear to be an excellent case study to consider whether diagnostic companies will invest more money in developing the clinical evidence base for a new test when they have greater certainty of a return on their investment.

Digene's 1999 annual report states that between 1995 and 1997 the company's R&D expenditure more than doubled from $1,856M to $4,131M and their 2003 annual report records R&D expenditure of $8,120M, $9,265M and $10,262M for the fiscal years 2001, 2002 and 2003 respectively.[145] Some of this expenditure would have been spent on Digene's other tests in the STD market and some would have been used for technical improvements to the HPV assay, but it seems likely that a significant proportion was invested in developing the clinical evidence base for the HPV test. In 2003 the company stated that:

> We have participated in human papillomavirus clinical trials involving an aggregate of approximately 90,000 women on four continents for which the final results are being prepared for publication. These studies have been conducted by prominent medical professionals and academic and government institutions throughout the world. A majority of the studies were designed to assess the usefulness of our HPV Test in comparison to the Pap test for women age 30 and over.[146]

As table 8 demonstrates, this process of collaboration involved partnerships with research charities, government departments, universities and public research institutes in North America, Latin America, Europe and China. Digene's contribution to these clinical studies varied: in some cases it took the form of research funding; in others the company provided their assay either at a heavy discount or free of charge. It would also have taken the form of providing expertise. For instance, Digene's Chief Scientific Officer Dr Attilla Lorincz who was one of the founders of the company, has played a leading role in elucidating the natural history of HPV infection having cloned and characterised several clinically important HPV types. He is the inventor on many of the key patents held by Digene and is a co-author on many of the scientific papers which have helped to build the evidence base for use of HPV testing.

One of Digene's early collaborations was with the managed care organisation Kaiser Permanente. They collaborated on a clinical trial in 1995-96 to illustrate the utility of the Digene test in triaging equivocal Pap smears. This study was jointly funded by the Kaiser Permanente Innovations Program and by grants, technical support, reagents, supplies, and equipment from Cytyc and Digene.[147] The clinical utility of this triage application was then investigated further in a far larger study funded by the National Cancer Institute - the 1996/98 ASCUS/LSIL Triage Study (ALTS trial). In this case Digene are listed as one of several companies who provided supplies or equipment at no cost or reduced cost. The completion of the ALTS trial was swiftly followed in 1999 by FDA approval for Digene's HPV test for testing women with abnormal Pap test results to determine whether they needed to be referred for further examination. The ALTS trial is also seen as the pivotal study which provided the basis for the de-

[145] Digene. 1999 Annual report; 2003 Annual Report, accessed online at: http://www.getfilings.com/o0000950133-03-003226.html
[146] Digene. 2003 Annual Report, accessed online at: http://www.getfilings.com/o0000950133-03-003226.html
[147] M. Michele Manos; Walter K. Kinney; Leo B. Hurley; et al. (1999) Identifying women with cervical neoplasia: using Human Papillomavirus DNA testing for equivocal Papanicolaou results *JAMA* 281(17):1605-1610

velopment of guidelines by ACOG and ACSSP and its importance was attested to by our US interviewees: “It validated the performance of the test in predicting CIN 3. It was such a widespread study and the recommendations based on that through ACSSP pretty much directed the growth of that test.”(US LAB 2)

Table 8 HPV clinical trials in which Digene was a participant in late 1990s

Country	Lead Investigator	Trial description	Size	Completion date
United States	National Cancer Institute	ALTS Borderline Pap Trial	7, 000	Completed
Canada	Newfoundland Department of Health	HPV Primary Screening	3,000	Completed
Mexico	Johns Hopkins; Mexican Government	HPV Primary Screening	7,500	December 1999
Netherlands	Free University of Amsterdam	HPV Primary Screening	40,000	December 2001
United Kingdom	Imperial Cancer Research Fund	HPV Primary Screening	10,000	December 2000
Germany	University of Tubingen	HPV Primary Screening	8,000	June 2000
Russia	University of Turku, Finland	HPV Primary Screening	12,000	December 2001
Brazil	University of Rio Grande do Sul	HPV Primary Screening	2,000	December 2000
Argentina	Institut Papincolau	HPV Primary Screening	1,000	Completed
Costa Rica	National Cancer Institute	HPV Primary Screening	10,000	Completed
China	Cleveland Clinic Foundation	HPV Primary Screening	2,500	November 1999

Source: Digene Annual Report 1999

Its use for triage of ASCUS cases was the low-hanging fruit of HPV testing. It exploited the chief weakness of pap testing, without challenging its status as the gold standard. However, this triage indication gave Digene only a small part of the cervical screening market. Digene then moved on to trials focused on demonstrating the utility of HPV testing as a routine adjunctive screen alongside the pap test. In 2003 Digene gained FDA approval for this new indication, allowing the test to be used for primary screening in conjunction with the Pap test, in women over age 30. However, even as Digene was pursuing this broader indication, it was funding trials which came to more radical conclusions. One such study was the HART trial in the UK, funded by Digene and led by Professor Jack Cuzick at the Imperial Cancer Research Fund. The study’s findings were published in a 2003 Lancet paper where the authors argued that Digene’s test could be used as a primary screen with pap testing as the follow-up for women testing positive.[148] The US kitmaker we interviewed suggested that this market was the one that other companies were interested in: “All the players in the market are betting on the transition to a model where all women get the [HPV] test. This would increase the size of the market by ten fold.” (US kitmaker). This approach has yet to be officially endorsed in guidelines, nor would it appear that Digene have sought FDA approval for this as an indication/intended use. Leading figures in the research community are calling for large-scale clini-

[148] Cuzick J et al. (2003) Management of women who test positive for high-risk types of human papillomavirus: the HART study. *Lancet* 362:1871–6.

cal trials to test its effectiveness,[149] and Digene have stated that in certain countries they are marketing their test "as a primary cervical screen, either in conjunction with, or separate from, the Pap smear." This approach has been endorsed by the World Health Organisation, because many developing countries lack the infrastructure to establish a cytology programme.[150] Digene are now collaborating with PATH on a kit specifically for this market.

Crucial factors in the diffusion of the test and rapid growth in usage has been availability of an FDA-approved kit with a significant amount of clinical data to support its use. A US kitmaker tied the evidence base to Digene's IP position: "Digene used their patent position to keep others from entering the market. This was an incentive to spend millions on postmarket studies and improve their assays." (US kitmaker). This evidence base is closely tied to the use of the Digene kit as it was their test which was used in key studies like the ALTS trial. One US interviewee saw this as Digene's key competitive advantage: "The next test won't have that scale of validation – a multi-institution, blinded, three-armed approach to clinical validation – that is their biggest advantage. The ALTS trial and ACSSP guidelines defined how to use HPV, if you are the test which defined it, that's going to be a hard act to follow." (US Lab2) One interviewee described Digene's role in studies such as the ALTS trial in negative terms: "essentially they were in bed with the people who were doing the study" (US Lab1)

In this regard it should be noted that the process of FDA approval has also set a benchmark which other companies must follow, at least in the US, where it is now broadly accepted that tests must have FDA approval to have any credibility. This argument was set out in the ACSSP guidelines: "[The] bar has been raised for bringing forward newer HPV diagnostics ... Any new test must document its performance relative to this standard"[151] and reiterated in the 2006 guidelines:

> These Guidelines expand clinical indications for HPV testing based on studies using validated HPV assays. One cannot assume that management decisions that are based on results of HPV tests that have not been similarly validated will result in the outcomes that are intended by these guidelines. Furthermore the application of these guidelines using such [unvalidated] tests may increase the potential for patient harm. The appropriate use of these guidelines requires laboratories utilize only HPV tests that have been analytically and clinically validated with proven acceptable reproducibility, clinical sensitivity, specificity and positive and negative predictive values for cervical cancer and verified precancer (CIN [cervical intraepithelial neoplasia] 2,3), as documented by U.S. Food and Drug Administration (FDA) approval and/or publication in peer-reviewed scientific literature.[152]

The US kitmaker we interviewed indicated the twin advantage offered by FDA approval, acting not only as a external validation of their test but creating a barrier to market entry: "Digene set the bar very high and FDA have kept it high." (US kitmaker). This interviewee suggested that FDA was asking all companies to do 10,000 patient trials, although it would appear that Third Wave/Hologic's Cerista HPV/HR test gained approval based on a trial involving approximately 4,000 women and Gen-Probe have indicated that their US clinical trials will seek to enrol approximately 7,000 women.[153]

Controversy about the use of tests which have not been approved by FDA, either using ASRs produced by rival kitmakers or LDTs, was raised in an article in CAP Today in 2005. The arti-

[149] Cox, T and Cuzick, J (2006) HPV DNA testing in cervical cancer screening: From evidence to policies. *Gynecologic Oncology* 103: 8–11
[150] IARC, WHO, IARC Handbooks of Cancer Prevention: Volume 10, *Cervical Cancer Screening* (Lyon, France: IARC Press, 2005).
[151] Wright, T et al. (2002) 2001 Consensus guidelines for the management of women with cervical cytological abnormalities *JAMA*. 287(16):2120-2129
[152] Wright, T et al. (2007) 2006 Consensus guidelines for the management of women with abnormal cervical cancer screening tests. *American Journal of Obstetrics & Gynecology* October: 346-355
[153] Hologic. FDA approves two Hologic HPV tests. Hologic press release, 13 March 2009. Gen-Probe. October 2008 Quarterly Report. Accessed online at http://biz.yahoo.com/e/081031/gpro10-q.html

cle was prompted by complaints by Dr Marc Schiffman, the National Cancer Institute's leading expert on HPV testing, who stated: "I do not want to see decades of careful research lessened in their impact by sloppy application or sloppy thinking. If a well-meaning laboratory applies an HPV test that doesn't work right, then a beneficial technology has just been made malignant." Also commenting on the issue was Dr Atilla Lorincz, Digene's CSO: "We spent tens of millions of dollars validating this test. For someone to come along and run 70 or 80 patients verges on the insult to everybody." He suggested that proper validation could cost from a few hundred thousand dollars to perhaps a few million dollars, and argued that since cervical screening was not an esoteric test then the scale of use justified a high hurdle, both because of the revenue which testing generates and the potential for harm from poorly-validated tests.[154] The company's position was reiterated in a 2006 commentary in the industry magazine IVD Technology, where Lorincz and Mark del Vechio, VP of regulatory and clinical affairs, criticised both the lack of regulation of LDTs in the US and the generally lax regulatory regime in the European Union. The company advocated a more consistent approach to regulation to support those companies who are committed to rigorous scientific validation of their products:

> … some industry members have made significant efforts to demonstrate and improve the value of diagnostics. Of particular concern is the inconsistent worldwide patchwork of regulations that seems inadequate to ensure the overall reliability and accuracy of test results as more tests are developed, and to foster a clear understanding of the clinical value of the results.[3] Such confusion allows test results to be provided unknowingly to patients through their doctors, even though their performance and clinical usefulness have not been extensively evaluated. [155]

Again they focused particular attention on the lack of FDA approval for LDTs:

> Since the clinical performance and utility of home brews are not subject to a level of scientific rigor as stringent as that which FDA applies to tests developed by IVD manufacturers, the true clinical value and consistent performance of many home brews remain unproven.[156]

It would appear then that Digene/Qiagen have adopted a dual strategy for building and protecting their near-monopoly status in the HPV market. In the US they have sued kitmakers for patent infringement but in relation to LDTs and companies marketing only in Europe, their approach has been to question the quality of scientific and clinical validation supporting the tests, pointing to their FDA approval as definitive external validation of the quality of their test. This emphasis on the need to use tests which have been FDA approved or whose validation has been subject to the peer-review process is in stark contrast to the widespread use of LDTs by the clinical genetics community (as illustrated by our Factor V Leiden case study).

4.3.2.4 Creating a market – promotional activities

Digene has driven market uptake with a major investment in sales and marketing, particularly in the US. Their 2006 annual report describes five strands to these promotional efforts:

1. gaining support of governmental agencies, medical societies and physician groups regarding the efficacy of HPV testing
2. working with laboratory partners to market the test to physicians and payors.

[154] Titus, K (2005) Making a valid point about HPV tests. *CAP Today* September: 76–82.
[155] Lorincz, A and del Vecchio, M (2006) Ensuring accurate diagnoses: Challenges from the manufacturing floor to the exam room *IVD Technology* July
[156] Lorincz, A and del Vecchio, M (2006) Ensuring accurate diagnoses: Challenges from the manufacturing floor to the exam room *IVD Technology* July

3. physician education programs, which are driven by our physician detailing organization and third-party organizations, working independently, to educate physicians and women about the proper use of the combined tests.
4. establishing comprehensive health insurance reimbursement for their tests
5. partnering with women's advocacy groups, and use of direct-to-consumer awareness campaigns to educate the public[157]

What is innovative about their approach is who they have targeted. The traditional marketing route for diagnostics has been to enroll the support of laboratory directors who would then promote the test to physicians. In the US this might also involve gaining the support of the major national reference laboratories, each of whom has their own sales force. Digene have not eschewed this traditional approach, but they have supplemented it with other techniques, in particular a sales force who work directly with physicians and the use of direct-to-consumer marketing. One US interviewee suggested that Digene's promotional strategy followed a model established by Cytc, makers of a Liquid Based Cytology test: "Cytc went directly to doctors and patients, we saw things in women's magazines and … they sent their sales force to ordering phsysicians. So Cytc drover that and then HPV fell right into that mode." (US Lab 2). Digene's PR campaigns have resulted in favourable editorial coverage for the test and the company also embarked on a major direct-to-consumer advertising campaign. The use of consumer advertising echoes activity by Myriad Genetics in promoting the BRCA test. DTC marketing in the media was supported by the use of branded educational websites such as Thehpvtest.com and Puttingwomenshealthfirst.org.[158] Digene have sought to enlist third parties such as the American Cancer Society and the Gynecologic Cancer Foundation and have provided grants to support the campaigns of nongovernmental organisations.[159] In our European interviews laboratory directors and a clinician mentioned that the commercialisation strategy could be considered successful (EU LAB1; EU LAB2; EU CLINICIAN). They also considered the work done to raise awareness about cervical cancer for women as an additional indication of this but concerns were expressed that the test is still underutilized and many respondents mentioned that more efforts should be done to encourage its diffusion (EU -LAB1; EU LAB2).

Whilst this activity can be seen as legitimate awareness building for a useful new test, some of our interviewees expressed concerns about Digene's promotional activities: one described the company's approach as "very aggressive" (US Lab 1), another stated that it was a major factor in inappropriate use of the low risk test which has no clinical utility: "the sales people are directly marketing to patients, so the patient comes in to the doctor and says 'I want this test', and the then doctor is in a void of education, so the doctor turns to the sales people who say 'Order this test – both of them ... you're not doing any harm, you can do it all off one vial.'" (US Lab2). Concerns were less apparent amongst European interviewees although one described Digene as "very, very pushy, especially in the United States" (UK clinician). However, this interviewee also suggested that the company had realised that such an approach was not going to facilitate adoption of the test in the UK. There has also been some public controversy surrounding the activities of a group called European Women for HPV Testing who have advocated use of HPV testing as a primary screening tool in all EU member states. In the UK The Observer newspaper reported in 2004 that the organisation had been established by Digene's PR consultancy Burston-Marsteller.[160] The UK branch of this group had begun lobbying for use of the test as early as 1999 and some British screening experts have argued that this advocacy was premature, since at the time evidence suggested that, in the context of the UK screening programme, use of Digene's test would have had no positive impact on mortality rates and would have led to an increase in the number of women harmed through over detection.[161]

[157] Digene. 2006 Annual Report.
[158] Bersch, C (2003) Digene's chairman/CEO Evan Jones discusses disease-specific molecular diagnostic tests, women's health issues and consumer health advocacy. *Medical Laboratory Observer* July
[159] Bersch, C (2003) Digene's chairman/CEO Evan Jones discusses disease-specific molecular diagnostic tests, women's health issues and consumer health advocacy. *Medical Laboratory Observer* July
[160] Barnett, A (2004) Revealed: how stars were hijacked to boost health company's profits. *The Observer* 25 January
[161] Raffle, A and Gray, M (2007) *Screening – Evidence and Practice* (Oxford University Press) 241-2

4.4 HPV test availability and usage

HPV testing has now become a standard of care in the US and is widely available in the Germany and Netherlands. Use of the test in the UK is far more limited where a large-scale evaluation of its potentially utility in the national cervical cancer screening programme is just being completed. The dominant test in use is the Digene Hybrid Capture kit, but others are available. (see table 9)

Table 9 HPV test kits in US and Europe

Manufacturer	Test name	Method	Market availability
Access Genetics*			US only?
Autogenomics	INFINITI HPV Genotyping	PCR	US? (Research Use Only)
DakoCytomation	GenPoint HPV Probe	ISH	Europe
Digene (now Qiagen)	HC2 HR and LR HC2 HPV HR HC2 DNA with Pap CareHPV	Hybrid Capture	US/Europe Will be used in developing countries
Gen-Probe	Aptimer	mRna	Europe
GenoID	Reveal HPV Full Spectrum HPV	PCR PCR	Europe
Greiner Bio-One	PappiloCheck	PCR	Europe
Innogenetics	INNO-LiPA	PCR	Europe
Kreatech	Rembrandt	ISH	Europe / US (through Zymed)**
Roche	Amplicor Linear Array	PCR	Europe
Third Wave/Hologic	Cerista HPV HR Cerista HPV 16/18	Signal amplification	Europe/US
Sensigen	AttoSense HPV Assay	Viral load	US (Research Use Only)
Ventana (now acquired by Roche)	Inform	ISH	US

*Access Genetics have a business model which they describe as a service, however, FDA have indicated to the company that they consider them to be selling medical devices (although it would appear that this has not led to the withdrawal of their products neither have the company sought FDA approval)
** This product would appear to be Research Use Only and it is not clear whether Kreatech are still operating.

4.4.1 HPV test availability and usage in the United States

The first HPV test kit to gain FDA approval was Life Technologies Virapap test in 1988. However, it is unclear whether there was significant uptake of this test. One leading US lab director we interviewed indicated no awareness of the Virapap test, suggesting that the *absence* of an FDA approved test meant that people were reluctant to use HPV testing in the 1990s (US Lab 2). This interviewee stated that prior to the approval of the Digene test in 1999 HPV testing was being used “quite haphazardly” and was only available from a small number of labs producing their own LDTs.

Availability and usage of HPV testing has grown rapidly in the United States since Digene launched their test in 2000. Most insurance companies now cover HPV testing. A number of states (California, Maryland, New Mexico, North Carolina, Texas and West Virginia) *mandate* private health insurers to cover HPV testing as recommended by clinical guidelines. Most states also cover HPV testing through their Medicaid programs. Industry figures suggest that

more than 10 million HPV tests are performed annually in the US, and the market for testing has been growing by 40 percent in each of the past five years. A recent CAP study found that all the labs in its survey offered the test compare with only 80% in 2003. However, not all these labs actually perform the test – 73% of cytology labs send their samples to larger reference labs.[162]

As noted in the previous section, Digene has enjoyed a near-monopoly in the United States since FDA approval of its test in 2000. However, there are alternatives to the Digene test in the US (see table above). Recent research comparing HPV testing trends in cytology labs between 2003 and 2006 reveals increasing use of non-Digene tests (19.1% labs in 2006, up from 12.8% in 2003).[163] For those labs who wish to use an alternative to the Digene test there are various options. Both Ventana and Third Wave sell Analyte Specific Reagents for HPV tests (TW's ASRs are now presumably to be discontinued since they gained FDA approval for their kits in March 2009). As noted earlier Third Wave state that they have about two per cent of the US market whilst the CAP 2006 survey suggest that eight per cent of labs are using Ventana's ISH test. Alternatively labs can produce their own test.

Whilst the ACOG/ACSSP guidelines have been seen as critical in driving uptake, recent research suggests that many physicians and labs fail to follow the guidelines. A 2006 CAP survey showed that 45% of labs provide testing for low-risk HPV strains despite no endorsement for this by the established guidelines. One US lab director interviewed commented on this stating that "there are a lot of wasted resources spent of a kind of worthless test". (US Lab 2) This interviewee also indicated that their lab continues to receive requests from doctors and nurse practitioners for HPV testing in women under 30 where it is not indicated and that doctors are not following the recommended protocol for patients *over* 30 who test negative for both the pap and HPV test. Guidelines state that the purpose of performing both tests together in this age group is to lengthen the time between repeat tests from one year (current US practice) to three years, but many continue to test their patients every year: "many physicians don't want to lose their patients over those three years, so they will have them come in every year, you know to do the mammogram, colonoscopy or whatever, but they'll continue to do the pap and HPV test, when the only reason to do the HPV test as a co-test in that age group is to lengthen the interval of screening." (US Lab 2)

However, alongside this evidence of inappropriate or over-utilisation, there is also evidence of under-utilisation. It is estimated that the U.S. market for HPV testing still has considerable potential for growth having only reached 28 percent penetration.[164] The 2006 CAP survey revealed that only 25 percent of labs offer combined Pap plus HPV testing for women over 30. Dr Nicholas Nolte, a US lab director with a keen interested in HPV testing stated in 2007 that clinicians in his own institution had not changed their screening practices in the light of recommendations for use of HPV as a primary screen and CDC HPV expert Elizabeth Unger predicted that many clinicians still feel most comfortable with Pap testing: "There are still people out there looking for a Pap test with increased sensitivity."[165]

According to one lab director the price they charge for testing varies depending on the rate negotiated by different insurance companies but generally ranges from $40 to $70, although it might be as high as $100 in the case of direct billing. They also commented that the test is fairly expensive to perform, but that Digene's monopoly position was not the primary reason:

> Well obviously without competition they're definitely going to be the most expensive on the block, I think what makes it expensive, though, is the labour. You need a skilled per-

[162] Moriarty AT et al. (2008) Human papillomavirus testing and reporting rates: practices of participants in the College of American Pathologists' Interlaboratory Comparison Program in Gynecologic Cytology in 2006. *Arch Pathol Lab Med.* 132: 1290–1294

[163] Moriarty AT et al. (2008) Human papillomavirus testing and reporting rates: practices of participants in the College of American Pathologists' Interlaboratory Comparison Program in Gynecologic Cytology in 2006. *Arch Pathol Lab Med.* 132: 1290–1294

[164] Third Wave Countersues Digene for Alleged 'Monopolistic Abuse' and Seeks $20 Million March 07, 2007 *GenomeWeb Daily News*

[165] Levenson, D (2007) New HPV test brings challenges *Clinical Laboratory News* 33(6): 1-9

son, so it can be a seven-hour test for 80 samples, so the more automated it becomes, the cheaper it will be for labs to do.

None of our US interviewees felt that price was affecting patient access, but there was concern about lack of access to alternatives to the HC2 test, in particular a desire for FDA-approved genotyping tests. This is a concern that has also been expressed by others: "The lack of multiple, competitive, well-validated tests" for HPV assay is quoted as being "a problem" in formulating new guidelines in management of cervical abnormalities."[166]

4.4.2 HPV test availability and usage in Europe

As noted earlier, there is a greater range of tests available on the European market than there are in the United States. This is not the only difference between the two markets. Digene entered the European market in 1997, three years earlier than it launched in the US but has still to gain widespread adoption in key markets such as the UK. In their 2006 annual report Digene stated that the European market presents them with a number of challenges including:

1. the lack of clinical guidelines and/or government public funding for HPV primary screening;
2. strong resistance from some current participants in the pathology, cytology and gynecology infrastructure to HPV testing;
3. limited reimbursement in certain countries; and
4. competition from emerging, non-validated technologies.[167]

4.4.2.1 Germany

Although other assays are emerging, the main tests for HPV available in Germany are Digene's Hybrid Capture 2 test and Roche's Amplicor HPV Test and Linear Array HPV Genotyping Test (the Amplicor test has been available in Europe since 2004). The recent Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V. (German Society for Gynaecology and Obstetrics) guideline on cervical cancer and HPV mentions both the Hybrid Cycle 2 and PCR genetic tests, as well as the cytological test. The society recommends genetic HPV testing for abnormal reports following the primary cytological screening for women of up to 30 years old. It considers the HC2 and PCR to have significantly higher sensitivity, although worse specificity then the cytological test. The guideline further provides a standard procedure for combining both cytology and HPV testing, monitoring developments over up to 12 months in a case of an initial abnormal cytology report through screening. In general, the guideline seems to favour HC2 testing over PCR tools (DGGG et al., 2008). The DGGG's guideline represents the most up-to-date position (March 2008) of the society on HPV testing. A previous guideline from this society was developed in collaboration with the Deutsche Krebsgesellschaft e.V. (German Cancer Society) and also mentioned DNA testing options (DKG and DGGG, 2004). Finally, a guideline on HPV from the Deutsche Gesellschaft für Urologie (German Society for Urology) also mentions HPV testing (DGU, 2001).

Digene's hybrid capture 2 test was the first HPV test to enter the German market, and a respondent mentioned that its introduction took place between 1996 and 2000 (EU LAB2). It is also perceived as the most highly used assay in Germany, as well as being a "global assay" that is being used in most published studies. The PCR tests were felt to be less used (EU LAB2). In 2006 Digene announced that Deutsche BKK, a major public-health insurance provider in central Germany, in partnership with the local gynecologists' association and a regional hospital was to launch Europe's first cervical cancer screening program using routine HPV testing.[168]

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[166] Stoler, M et al (2007) The expanded use of HPV Testing in gynecologic practice per ASCCP-guided management requires the use of well-validated assays *American Jounal of Clinical Pathology* December

[167] Digene. 2006 Annual Report.

[168] http://web.archive.org/web/20061023234925/investor.digene.com/phoenix.zhtml?c=82439&p=irol-newsArticle&ID=803413&highlight=

In Germany public insurers will reimburse for use of the test with an abnormal Pap test, and a small number of patients also pay for the DNA test themselves. One commercial laboratory issued between 5,000 and 10,000 reports for HPV a year (EU LAB2) and the other 2,000 reports a year, although this was its only testing activities (EU LAB1). German interviewees felt that HPV tests are now widely used, but that they were still behind cytological tests in use, and several respondents commented that more efforts should be done to encourage its diffusion (EU -LAB1; EU LAB2). As will be seen below, there currently appears to be a conflict between gynaecologists and geneticists on which test to use. In one case, this led a respondent to consider HPV testing as being only partially accepted (EU LAB1).

Roche's genotyping assay was used by one laboratory, but only as a follow-up to the Digene test in cases where they felt that genotyping might be helpful. This was not done very often, and it was considered to be an expensive test to perform (EU -LAB2). Interviewees stated that the Pap smear cytology test was has a much lower sensitivity. Pap smears were still considered more widely used in Germany, despite one's respondent opinion that there are known deficiencies in the area of cytology in the country. Laboratory directors interviewed stated that gynaecologists limit their referral of patients to HPV testing in order to protect the income coming from their cytological testing activities (EU LAB1; EU -LAB2). This observation would seem to support Digene's contention that uptake of HPV testing in Europe is inhibited by entrenched interests of certain professional groups (see above)

Costs for performing the tests for the labs varied from 40€ to much above 66€ (using different kits). In the first case, reimbursement from insurers in cases with an abnormal cytology was 20€ (EU -LAB1; EU Lab2).

4.4.2.2 Netherlands

HPV genetic testing for research has been in use in the Netherlands and its use in clinical practice has become more frequent in the last five years. Clinical guidelines for use of HPV testing were established by the Dutch Organisation of Clinical Pathology, the Dutch Organisation of General Practitioners and the Dutch Society of Gynaecologists in 2006-2007. Patients are always reimbursed for HPV testing if the protocol is followed. Patients are not involved in the decision to access the test. It is the clinician who makes the decision.

There are a number of tests available, both LDTs and test kits. There is widespread use of the Digene test but interviewees indicated interest in genotyping technologies as well.

4.4.2.3 United Kingdom

The UK is the only country in our sample which has not adopted HPV testing on a wide scale. There would not appear to be any clinical guidelines from professional groups in the UK regarding the use of HPV testing, suggesting that clinicians and pathologists accept that adoption of HPV testing cannot be ad hoc or opportunistic but has to come through changes to the UK Cervical Screening Programme (UKCSP) is a decision for the National Screening Committee. This is certainly the implication of the 2006 scientific statement on cervical cancer screening published by the Royal College of Gynaecologists which states that "The UKCSP necessitates a degree of conservatism, as any change requires to be solidly evidence based and to be implemented nationally, which therefore, involves considerable upheaval." However, the statement suggests that it is likely that HPV testing for borderline cytology would be a useful addition to the current national screening programme and that its potential in primary screening should become clearer as the findings from a number of large randomized trials in a number of European countries is published.[169]

As early as 1999 an HTA report had indicated the potential of HPV testing and the National Screening Committee requested further evidence. Since then a series of studies have been conducted to evaluate use of HPV testing within the NHS Cervical Screening Programme. The TOMBOLA study began in 1999 and was a seven year multi-centre trial to determine the most appropriate way to deal with HPV positive results and associated psychological issues.

[169] Royal College of Obstetricians and Gynaecologists (2006) Progress in cervical cancer screening. SAC Opinion paper 7 June

The ARTISTIC study began in 2001 and is a randomised trial of HPV testing in primary cervical screening and involves 25,000 women aged 20-64 who are attending general practices for routine cervical screening. The study aims to:

- provide clear evidence on the costs, medical effects and psychosocial impact of adding HPV testing to cervical cytology
- provide an estimate of the effectiveness and costs of HPV as a stand-alone test
- determine the contribution of HPV detection to the cervical screening programme, particularly to sensitivity, specificity and inadequate smears
- address methodological issues in HPV testing

Separate screening pilots are being conducted to evaluate the use of HPV testing for triage of abnormal LBC results and for test of cure. Results from these pilots are likely to available in late 2009, results from the ARTISTIC trial are expected earlier in 2009. All these studies have been conducted using the Digene test. In the meantime the major development in the UK's cervical cancer screening programme in recent years has been the move to liquid-based cytology in place of the traditional Pap test. Adoption of LBC has facilitated the piloting of HPV testing and our UK interviewee considered it probable that the use HPV for triaging and test of cure will be adopted in the NHS. Its future use as an adjunctive primary screening test seems less certain. An alternative option which our interviewee suggested might be more likely is the replacement of LBC testing with HPV testing, although such a dramatic shift would require very good evidence for increased detection rates and greater cost-effectiveness. Our interviewee did not consider that cost would prohibit the use of HPV testing, as the potential value of a national contract would allow the NHS to negotiate a competitive price for the test.

Whilst there has been no adoption within the NHS, HPV testing is available outside the NHS as part of a general health screen for women offered by the private healthcare provider BMI and through a number of private labs.[170] In some cases it is not clear which tests are being offered by these labs, although one offers both genotyping and mRNA testing (believed to be done with the NorChip test). Another private lab eschews HPV testing but offers TriPath's ProEx test.

4.5 The clinical utility and cost-effectiveness of HPV testing

4.5.1 Cytology screening

Screening for cervical cancer has traditionally been based on cytological techniques. Cytological screening has had a major impact on lowering cervical cancer rates in many countries, indeed a recent review article describes it as “the most effective screening test for cancer that has ever been devised.”[171] The RCOG state that in the UK the move to a systematic national screening programme in 1988 has had significant benefits:

> The programme has had a dramatic effect, with a falling incidence of death from cervical cancer: the death rate is now just 50% of what it was in 1988. It is estimated that 2,000 lives a year are saved, many in young women. The annual expenditure of £130 million consumed by the NHSCSP is viewed as highly cost effective. Similar falls in death rates have been seen in Finland, Iceland and the USA.

These cytology-based screening programmes have two main weaknesses. The first is the failure to recruit all women – 50% of cervical cancers diagnosed in the US involve women who have never been screened, another 10% involve women who have not been screened for at least five years.[172] The second weakness is in the cytological techniques used. The Pap

[170] BMI website. Health Assessment. Accessed online at http://www.bmihealthcare.co.uk/health-screening/general_investigations#Cervical
[171] Dehn, D et al (2007) Human papillomavirus testing and molecular markers of cervical dysplasia and carcinoma. *Cancer* 111(1):1-14.
[172] Saslow, D et al (2002) American Cancer Society guideline for the early detection of cervical neoplasia and cancer *CA Cancer J Clin* 52(6): 342-362

test is based on an examination of cervical epithelial cells for atypical physical abnormalities that are indicative of cancer or a precancerous condition. The Pap test relies solely on the visual examination of cells under a microscope, requires highly trained personnel and specialized equipment and is expensive to perform. The limitations of cytology are set out in a 2006 paper by Cox and Cuzick:

1. Results are dependent on a high quality sample being collected at examination
2. The reading of the slide is subjective
3. The repetitive nature of the reading, which can lead to greater number of interpretive errors[173]

The new liquid-based cytology tests have improved this by providing easier to read slides. Assessment of this technology in the UK indicated that "inadequate cytology would be cut by 80%, that laboratories could process slides more quickly and that, despite increased costs per slide, overall liquid-based cytology would be cost effective."[174] However, from a clinical perspective the major limitation of cytology-based screening continues to be its limited sensitivity – sensitivity is 50-70% to detect CIN3[175] and 48-57% to detect CIN2+.[176] In order to compensate for poor sensitivity it is necessary to identify and act on minor cellular abnormalities. The ACSSP 2001 guidelines state that 50 million women have Pap tests each year in the US and that 7% (about 3.5 million) are diagnosed with a cytological abnormality requiring additional follow-up or evaluation i.e. smears diagnosed with ASCUS (atypical squamous cell of unknown significance), atypical squamous cells suspicious cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), or atypical glandular cells (AGC).[177]

One widely used option for dealing with such results are to repeat cytological testing at specified intervals, following up with colposcopic biopsy if malignancies are detected. This approach has a number of disadvantages: "It can delay the diagnosis of CIN 2,3 or cervical cancer and, even in populations with good access to health care, adherence to recommendations becomes a problem for any follow-up that requires multiple visits."[178] Another way to manage ASCUS results is immediate referral for colposcopic biopsy. Disadvantages of this approach are it is uncomfortable, expensive, can raise unnecessary anxiety and may lead to overdiagnosis and overtreatment.[179] Furthermore although colposcopic biopsy has been the gold standard procedure for diagnosis of cervical cancer recent evidence suggests that this technique can miss as much as 50% of high-grade disease.[180] As indicated earlier, HPV testing provides an alternative means of dealing with these borderline results.

4.5.2 HPV testing

The ASCCP's 2001 Consensus Guidelines state that clinical data from ALTS and other studies had proved HPV DNA testing is a safe and effective means of triaging women with ASCUS. Although they acknowledge that repeat cytology and immediate coposcopy are acceptable alternatives, the guidelines state that reflex HPV DNA testing is the preferred approach. The key advantage of what they describe as 'Reflex HPV DNA testing' is that the sample is

[173] Cox, T and Cuzick, J (2006) HPV DNA testing in cervical cancer screening: From evidence to policies *Gynaecologic Oncology* 103: 8-11
[174] Royal College of Obstetricians and Gynaecologists (2006) Progress in cervical cancer screening. SAC Opinion paper 7 June
[175] Nanda K, et al (2000) Accuracy of the Papanicolaou test in screening for and follow up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med* 132:810–19.
[176] Cuzick, J et al (2006) Overview of the European and North American studies on HPV testing in primary cervical cancer screening *Int J Cancer* 119: 1095-101
[177] Wright, T et al (2002) 2001 Consensus guidelines for the management of women with cervical cytological abnormalities *JAMA*. 287(16):2120-2129
[178] Wright, T et al (2002) 2001 Consensus guidelines for the management of women with cervical cytological abnormalities *JAMA*. 287(16):2120-2129
[179] Wright, T et al (2002) 2001 Consensus guidelines for the management of women with cervical cytological abnormalities *JAMA*. 287(16):2120-2129
[180] Dehn, D et al (2007) Human papillomavirus testing and molecular markers of cervical dysplasia and carcinoma. *Cancer* 111(1):1-14.

collected at the time of the original screening test using either the LBC sample or a sample co-collected for HPV testing in case of ASCUS. The justification for this recommendation is as much about speed and convenience as it is about the predictive value of the test: "women do not need an additional clinical examination for specimen collection, and 40% to 60% of women will be spared a colposcopic examination. Moreover, women testing negative for HPV DNA can rapidly be assured that that they do not have a significant lesion."[181] The 2006 guidelines confirmed reflex HPV DNA testing as the preferred approach and provided additional justification from new data, stating that this approach: "spares 40-60% of women from undergoing colposcopy, and has been shown to have a favorable cost-effectiveness ratio."[182]

Both our US lab directors were using the Digene test in accordance with ACSSP guidelines, for ASCUS triage stating that it was a de facto standard of care (US Lab 1). Our UK interviewee suggested that it was only a matter of time before they adopted the use of HPV testing for ASCUS triage (and also for use as a test of cure). However, two Dutch interviewees, a clinician and a lab director suggested that HPV test is of limited use for borderline Pap results. (EU clinician 1, EU Lab1).

The second application of HPV testing is in primary screening. A recent overview analysed the findings of a number of different studies from Europe and North America where HPV testing was performed as a primary screen in parallel with cytology. The sensitivity of HPV testing was substantially greater in detecting CIN2+ than cytology (96.1% vs. 53.0%) but its specificity was poorer (90.7% vs. 96.3%).[183] The 2006 ASCCP guidelines note that combining HPV testing and cytology gives significantly greater sensitivity than the use of either test on its own, with negative predictive values of 99-100%. It is hoped that this new testing protocol could reduce the incidence of false-negatives, and allow less frequent screening for women who are negative on both Pap and high-risk HPV tests. These women would also benefit from the psychological reassurance that concurrent negative test results for Pap and HPV gives them a risk of cervical cancer of approximately 1/1000.[184] Health policy modeling studies of combined cytology and HPV testing in women 30 years and older, have shown that it need only be done every three years to provide equivalent or greater benefits than a yearly cytology test.[185]

Out interviews revealed a notable difference between the clinical utility of the HPV test in the US and in the UK because of their different protocols for cervical screening. In the US it has been standard practice to offer women a cytology test on an annual basis, and the addition of HPV testing in women over 30 allowed the recommendation to be changed to once every two years if both tests are negative. In the UK, by contrast, current practice is already to offer a liquid-based cytology test every two years to women between 25 and 50 and every five years to women between 50 and 64: "In this country the frequency of screening has not been a big issue so there is no particular advantage to using two tests together to lengthen interval screening." (EU clinician)

However, there are concerns about the use of HPV testing in primary screening as it is less specific than cytology, especially amongst younger women where transient HPV infection is relatively common but incidence of high grade lesions is low, hence the recommendation that HPV screening only be done in women 30 or older. Even in this group, however, the rate of false positives arising from HPV testing gives cause for concern, particularly about the "adverse psychological and psychosexual effects that HPV testing may induce in some women".[186]

[181] Wright, T et al.(2002) 2001 Consensus guidelines for the management of women with cervical cytological abnormalities *JAMA* 287(16):2120-2129
[182] Wright, T et al 2006
[183] Cuzick, J et al (2006) Overview of the European and North American studies on HPV testing in primary cervical cancer screening *International Journal of Cancer* 119(5): 1095-1101
[184] Cox, T and Cuzick, J (2006) HPV DNA testing in cervical cancer screening: From evidence to policies *Gynaecologic Oncology* 103 8-11
[185] Wright, T et al 2006
[186] Royal College of Obstetricians and Gynaecologists (2006) Progress in cervical cancer screening. SAC Opinion paper 7 June

Commenting on the cost-effectiveness of the HC2 test, at least one lab director complained that the test is too expensive, though suggested that the main cost is the labour: "You need a skilled person and it can be a seven-hour test for 80 samples." (US Lab 2) Digene claim that automation using a robotic instrument can increase throughput to 354 tests in one batch.[187]

4.5.3 HPV genotyping, viral load testing and other molecular markers

On its own the presence of HPV does not correlate well with progression to cancer. The fact that the Digene test does not distinguish between different high-risk strains is considered a drawback. One US lab director stated that there were problems with the Digene test concerning cross-reactivity with low-risk groups and unacceptably high false positive rates (US Lab 2) and suggested that as HPV vaccination is taken up, then disease prevalence will change, increasing the rate of false positives. There is increasing clinical interest in testing methods which may be more specific than the Digene test, and in particular growing use of genotyping for high-risk HPV strains, especially for HPV types 16 and 18, the most oncogenic HPV types. However, current use of genotyping is not as a screening test but as a confirmatory or differential diagnosis. The challenges of genotyping were raised by interviewees, in particular the technical demands of running PCR testing: "it is not a minor undertaking for a lab, it needs pretty exquisite, clean, exacting technology – a lot of places don't have the room or the people to do it. Unless PCR gets easier to implement in a standard lab it's not going to have as much impact." (US lab 2). Aside from technical difficulties, there are also doubts about the clinical significance of PCR "PCR can get down to very few copies of the virus but again we don't know what that means clinically." (US lab 2) Another US lab director described how they had developed their own homebrew PCR test in response to clinician demand: "It is very useful – obviously young women acquire different high-risk types and then resolve them, we want to be able to type the HPV to know if it's the same type or a new type." (US Lab 1) This is important because it is persistent infection with a high-risk strain which leads to cancer. Roche has two PCR-based genotyping products: the Amplicor HPV Test and the Linear Array HPV Genotyping Test. The Amplicor kit detects the presence of 13 high-risk strains of HPV. The Linear Array test identifies 37 HPV strains including all high- and low-risk genotypes in the anogenital region. Other genotyping kits include Gen-Probe's APTIMA HPV test and Hologic's Cervista HPV16/18 test which is the first HPV genotyping kit to gain FDA approval.

However, as noted earlier, even detecting high-risk HPV strains is of limited clinical utility because many infections are transient. Thus interest is growing in tests that can accurately predict individual women's risk of developing cervical cancer and which are able to identify specific precancerous stages.[188] These include:

- viral load testing
- surrogate markers, such as proliferative markers (p16 and mRNA) or cell cycle markers (cdc6 and mcm5 proteins)
- comparative genomic hybridization to identify host-cell biomarkers[189]

Viral load is associated with persistence of infection and disease progression. HPV viral load patents granted to the Swedish company Quantovir was acquired in 2007 by the US company Cepheid. Cepheid already produce FDA-approved molecular tests for other infectious diseases and the company have stated that they intend to use viral load to pursue a different approach to HPV screening. In September 2007 David Persing, executive vice president and chief medical and technical officer, told an industry conference that their approach will be to begin HPV screening much earlier - at age 18 rather than 30 as is recommended for the HCII test. Infected patients will receive repeat tests to measure viral load and track type-specific resistance over a period of time and to indicate whether a patient has a persistent infection.[190]

[187] Levenson, D (2007) A new era in cervical cancer screening. *Clinical Laboratory News* 33(6): 1-9
[188] Peck, R et al (2008) Human papillomavirus testing today and tomorrow *IVD Technology* November
[189] Wasserman, P; Schwartz, M; Darragh, P (2007) Understanding HPV testing's place in primary screening *CAP Today* January
[190] Winnick, E (2007) Cepheid Licenses IP to Develop Quantitative HPV MDx, Loses CDC Contract for Flu Test. *GenomeWeb* September 26, Accessed online at http://www.genomeweb.com/cepheid-licenses-ip-develop-quantitative-hpv-mdx-loses-cdc-contract-flu-test

Precancerous cell changes are associated with elevated levels of two HPV-encoded oncoproteins, E6 and E7, which disrupt the cell cycle by affecting cellular proteins such as p53 tumor suppressor and p16 kinase. Gen-Probe's APTIMA test combines genotyping of 14 high-risk HPV strains with detection of E6 and E7. The Norwegian company NorChip has also developed an mRNA test. A recent study comparing this test with PCR in women with an initial diagnosis of ASCUS or LSIL, found that it equal sensitivity but greater specificity than PCR, in diagnosing/predicting progression to CIN2+.[191] Our UK interviewee thought this approach had potential: "RNA expression may imply an active HPV infection, whereas DNA could just be a harmless passenger." (EU clinician2). An alternative approach is to identify genes which are over-expressed in cervical cancer, a method commercialised by the US company TriPath Imaging and the German company mtm Laboratories, whose tests identify elevated levels of $p16^{INK4a}$.

4.6 Lessons learned on the role of IP

The HPV case is one where there exists a very dense patent thicket involving patents granted to both public and private sector institutions. This IP has had a major impact on the shape of the US market which is dominated by Digene/Qiagen, the company who has managed to acquire, or gain exclusive licenses to, key patents, but its impact on the EU market is less clear. Like TMPT this is another case where there would appear to be significant differences between the US and the EU.

Digene's dominant position in the market place in the United States is in large part a function of its acquisition of core HPV patents. However, it is not the only factor. Rival companies are seeking FDA approval and, since HPV tests continue to be classified as Class III devices, they must go through the lengthy Pre Market Approval process. Companies such as Ventana have chosen to market their HPV test as ASRs rather than seeking FDA approval. It is worth noting in this respect that even Factor V Leiden tests in US are more often marketed as ASRs than FDA-approved kits (there are currently three FVL test kits approved by FDA). Both US lab directors stated that the market preference is for FDA approved tests and this may be more the case in infectious disease testing where many of the labs running tests do not have the specialist expertise of a molecular genetics laboratory.

Regardless of the range of commercial and regulatory factors that may be playing a role in the slow development of alternatives to the Digene test, there is no doubt that IP is a major factor

4.6.1 Patenting and access to testing for patients

The HPV case is one where strong patent enforcement would not appear to be affecting patient access to testing since there has been very broad uptake of the Digene test. One US interviewee expressed concern about the cost of the Digene test stating that it was expensive to perform and that the cost was in part a function of Digene's monopoly. However, they felt the main cost factors were in fact the time and labour required to run the test (US Lab 2). Another US lab director did express concern about the possible impact of test cost on patient access for women with no health insurance (US Lab 1).

Patient access was generally considered not to have been affected by IP in any way by German interviewees. One respondent mentioned that having assays produced by private companies with IP on their products ensured a better level of quality (EU LAB1), a sentiment shared by both US lab directors. IP could have a negative impact on test costs, which have a great impact on patient access, in the few cases where reimbursement is not provided (EU LAB1). According to a Dutch clinician and a Dutch lab director, patients' access to HPV genetic tests are not affected by patents. Patients might have been affected, to a certain extent, because of the delay in rival tests coming to market, in particular a Dutch interviewee men-

[191] Molden et al (2005) Predicting CIN2+ when detecting HPV mRNA and DNA by PreTect HPV-proofer and consensus PCR: a 2-year follow-up of women with ASCUS or LSIL Pap smear *Int J Cancer* 114: 973-976

tioned the development of a new genotyping test which is yet to be offered commercially. Clearly the situation in the UK is that patient access to HPV testing is limited to the private sector but that is a function of the need to generate robust evidence before altering the national cervical screening programme, so gene patents have not been a factor.

4.6.2 Patenting and innovation

Given the strength of Digene/Qiagen's patent position and their virtual monopoly on the US market since they launched the HC2 test nine years ago, this case is an excellent test of the theory biomarker IP may encourage diagnostic companies to invest more heavily in clinical studies for a new test. Certainly Digene/Qiagen have presented themselves as a model for the IVD industry with regard to robust test validation:

> The industry needs to decide if it wants to continue developing analytical tests for which someone else assumes the responsibility of demonstrating clinical validity and usefulness; or be more involved in producing value-added clinically accurate tests intended to be used in defined algorithms that convey a seal of quality and utility.[192]

Digene had played a key role in developing the clinical evidence base for their test providing the assays for studies such as the pivotal ALTS trial. But Digene was not the only company helping to build the evidence base for the clinical relevance of HPV. Roche supplied its linear array HPV test free to researchers.

The argument about biomarker IP and clinical evidence hinges on the free rider problem – the capacity of rival companies to exploit the clinical studies paid for by a pioneering firm. The question for Digene/Qiagen is how far it can maintain a dominant market position as rival tests emerge and whether it can continue to be the sole party capturing the value of their R&D investment. As the market matures the clinical evidence base developed by Digene may become a double-edged sword, on the one hand it may force other companies to invest heavily in clinical trials, as we have seen with Gen-Probe and Third Wave/Hologic. On the other hand, it becomes part of a broader evidence base demonstrating the value of HPV testing in general, and may prove equally useful to Digene/Qiagen's competitors. The most difficult challenge in driving clinical uptake may be the shift from cytology to molecular tests, and it is Digene/Qiagen who have driven that change. It remains to be seen whether other companies with rival tests will find the task of gaining market acceptance for a test which is an incremental improvement on the HC2 test far easier and far less costly.

It is with regard to this process of incremental improvement in HPV testing that our US lab directors expressed greatest concern about Digene/Qiagen's dominant position. The US is the most mature market for HPV testing and here the lab directors indicated a strong demand for alternatives such as genotyping which can address some of the limitations of the Digene test: "Other companies like Gen-Probe could have developed a better test" (US Lab 1); "Everyone is waiting in anticipation for FDA approval of the Third Wave test, because we view it as competition ... people want competition, it's much better to have a choice for lab users." (US Lab 2). A variety of factors were thought to be affecting the slow availability of rival tests: in the case of one leading company it was believed that IP negotiations with Digene had been an issue but that a series of changes in senior management had also delayed their entry to the market. It was understood that another US kit manufacturer had also been delayed by the need to negotiate with Digene (US Lab 1). However, both interviewees suggested that delay may also be caused by the FDA approval process "I guess the FDA has asked them for more and more data" (US Lab 1) "FDA is always changing their mind about something." (US Lab 2).

One of our US lab directors was concerned that IP was becoming a difficulty in the area of molecular oncology, particularly in the case of markers for which there is not yet an FDA-approved kit: "these are niche assays, it's very difficult to get approval to run it, sometimes

[192] Lorincz, A and del Vecchio, M (2006) Ensuring accurate diagnoses: challenges from the manufacturing floor to the exam room *IVD Technology* July

you can negotiate a set fee, but often you can't ... it's happening more and more, for instance ... a lot of these markers are patented even though people with the IP have no immediate desire to make them into assays – it's a huge problem in research." (US Lab 1).

The dilemma of this lab director engaged in academic research on new biomarkers serves as a reminder that the clinical evidence base for HPV testing has not emerged solely from private sector investment. It is not possible to provide figures for the level of public investment in this field, but from the initial discovery of the HPV16 strain academic researchers have led the field, as is demonstrated by the fact that key patents were granted to institutions such as Georgetown University and the Institut Pasteur. In the case of BRCA testing, critics of Myriad's patents argued that the private exploitation of public research was immoral, in the case of HPV there would appear to have been no such outcry - perhaps in part because it is clear that Digeen/Qiagen have made a major investment in R&D, but also because the lab community has welcomed the Digene test. Certainly all our US interviewees acknowledged that Digene had played a important role in driving uptake of HPV testing and that their success in gaining FDA approval had provided the market with an advance on the homebrew tests which were then available. One lab director who had been performing HPV testing with an LDT in the 1990s said: "We had developed a $50,000 test; they developed a $50m test." (US Lab 1).

4.6.3 Lessons from comparing the US and EU

There are significant differences between the US and Europe with regard to HPV testing. Digene/Qiagen have reported difficulties building market acceptance in Europe and of the three EU countries we have surveyed, the most profound failure has been in the UK, where HPV testing has yet to become part of the national screening programme for cervical cancer and the only uptake is in the private sector, a relatively minor part of the national healthcare market. It is to be expected that the company would focus primarily on its domestic market, given its size, familiarity and the trend towards early adoption of new technologies in the US. However, Digene/Qiagen have been active in trying to build a European market, and their failure to achieve greater uptake may be of concern given that many of their key patents are due to expire soon.

IP is also a significant difference between the US and EU, given the amount of patent litigation in the US and its absence in Europe. It is fair to assume that this is a major factor in the greater number of companies entering the European market compared with the US. . A number of explanations for this are possible. It may be that companies in Europe are entering into private licensing arrangements with Digene to avoid public litigation, although this seems unlikely since Digene/Qiagen have a dominant position in the European market which they presumably wish to protect. It is perhaps more likely that that Digene/Qiagen sees the US as its most lucrative market and is focusing its resources on protecting this market.

Another plausible theory is that European companies have developed tests whose technology does not infringe on Digene/Qiagen's patents. Some of Digene's IP (some of the patents licensed from Institut Pasteur and Georgetown University) have expired in the EU but not in the US, but if these are recent expirations then that would not explain why the company has not sued in past years. One of Digene's US patents (US5116734A) was filed in Europe as well (WO1991003718A1) but the application is deemed to be withdrawn. One US interviewee suggested that the key blocking patents are Digene's own patents on two high risk HPV types and that this IP is US only. (US kitmaker) We could not find the patents they referred to but this is due to difficulties associated with using the EPO database. Another possibility is that Digene has looked at the Myriad/BRCA story as a salutary lesson in the challenges of enforcing biomarker IP in Europe.

However, IP is not the only factor shaping differences between the US and European markets for HPV testing. Regulatory issues are also shaping the market. Given the far higher regulatory hurdle in the US, it is unsurprising that even US companies such as Gen-Probe and

Hologic/Third Wave are entering the European market first. This is a common pattern in the IVD market and in the medical devices sector more broadly. Given the lower barrier to market entry in Europe, it might be expected that Europeans would be more relaxed about whether or not a test has FDA approval, but it is noteworthy that even European guidelines, such as the consensus documents produced by the EUROGIN organisation, make reference to FDA approval as the gold standard of external validation of HPV tests.[193] Whether this influences choice of tests in Europe is another matter.

[193] Meijer CJ; Snijders, P and Castle, P (2006) Clinical utility of HPV genotyping *Gynecologic Oncology* 103: 12-17

4.3. Table 9 Human Papillomavirus (HPV) patents

Family	Patent	Status	Patent Number	Patent Country	Filing Date	Publication Date	Assignees	New Assignees	Inventors	Assignee Country	Title
1	Granted	Expired	US4849332*	US	26-5-1987	18-7-1989	LIFE TECHNOLOGIES INC [US]	DIGENE CORPORATION	LORINCZ ATTILA T [US]	US	Human papillomavirus 35 nucleic acid hybridization probes and methods for employing the same
1	Granted	Expired	US4849331*	US	9-6-1987	18-7-1989	LIFE TECHNOLOGIES INC [US]	DIGENE CORPORATION	LORINCZ ATTILA T [US]	US	Human papillomavirus 44 nucleic acid hybridization probes and methods for employing the same

1	Granted	Expired	US4849334*	US	9-6-1987	18-7-1989	LIFE TECH-NOLOGIES INC [US]	DIGENE CORPORA-TION	LORINCZ ATTILA T [US]	US	Human papil-lomavirus 43 nucleic acid hybridization probes and methods for employing the same
1	Granted	Expired	EP0294659*	DE GB NL	1988-05-26	1993-12-22	LIFE TECH-NOLOGIES INC [US]	DIGENE CORPORA-TION	LORINCZ ATTILA T [US]	US	Human papil-lomavirus nucleic acid hybridization probes and methods for employing the same
1	Granted	In force	US4908306*	US	27-4-1989	13-3-1990	LIFE TECH-NOLOGIES INC [US]	DIGENE CORPORA-TION	LORINCZ ATTILA T [US]	US	Human papil-lomavirus 56 nucleic acid hybridization probes and methods for employing the same

2	Granted	Lapsed	EP357611B1	DE GB NL	24-2-1988	19950426	The University Of Sydney		MORRIS BRIAN JAMES; NIGHTINGALE BRIAN	AU	A method of detection of carcinogenic human papillomavirus
2	Granted	In force	US5783412A	US	25-8-1989	19980721	BIOSEARCH INTERNATIONAL PTY LT [AU]	Polartechnics Ltd.	MORRIS BRIAN JAMES [AU]; NIGHTINGALE BRIAN [AU]	AU	Method of detection of carcinogenic human papillomavirus
2	Granted	In force	US6218104B1	US	30-12-1997	20010417	BIOSEARCH INTERNAT PTY LTD [US]	Polartechnics Ltd.	MORRIS BRIAN JAMES [AU]; NIGHTINGALE BRIAN [AU]	AU	Method of detection of carcinogenic human papillomavirus
2	Filed	RO Processing Completed-Placed In Storage	WO2001073135A2	DE GB NL US	27-3-2001	20011004	Biosearch International Pty. Ltd.|Molodysky, Eugen|Cord, Janet, I.		MOLODYSKY, Eugen	AU	Approaches for hpv detection and staging by targeting the e6 gene region of the viral genome

3	Filed	The application is deemed to be withdrawn	EP338067A1	DE GB NL	30-9-1988	19891025	Microprobe Corporation		SCHWARTZ DENNIS E; ADAMS TREVOR H	US	Human papillomavirus type diagnosis with nucleotide probes
4	Granted	Expired	EP0217919*	DE GB NL	1986-03-28	1992-08-05	Georgetown University		LANCASTER WAYNE D; JENSON BENNETT A	US	TYPE-SPECIFIC PAPILLOMAVIRUS DNA SEQUENCES AND PEPTIDES
4	Granted	In force	US5057411*	US	1-5-1989	15-10-1991	Georgetown University		LANCASTER WAYNE D [US]; JENSON A BENNETT [US]	US	Type-specific papillomavirus DNA sequences and peptides
5	Granted	In force	EP433396B1	DE GB NL	29-8-1989	19960515	CETUS CORP [US]	F. Hoffmann La Roche AG	MANOS M MICHELE [US]; WRIGHT DEANN K [US] (+3)	CH	Detection of human papillomavirus by the polymerase chain reaction

5	Granted	EXPIRED DUE TO FAILURE TO PAY MAIN-TENANCE FEE	US5283171A	US	15-2-1991	19940201	Hoffmann La Roche Inc.|The University of Rochester, New York	MANOS M MICHELE [US]; WRIGHT DEANN K [US] (+3)	US	Compositions for and de-tection of human papil-lomavirus by specific oli-gonucleotide polymerase primers using the poly-merase chain reaction
5	Granted	In force	US5447839A	US	20-4-1993	19950905	Hoffmann La Roche Inc.	MANOS M MICHELE [US]; BAUER HEIDI M [US] (+3)	US	Detection of human papil-lomavirus by the poly-merase chain reaction
6	Granted	In force	EP0370625	DE GB NL	24-10-1989	19940914	Georgetown University	LANCASTER WAYNE D	US	Human papil-lomavirus type 52 DNA sequences and methods for employing the same

6	Granted	In force	US5643715	US	23-3-1994	19970701	Georgetown University	LANCASTER WAYNE D	US	Human papillomavirus type 52 DNA sequences and methods for employing the same
7	Granted	In force	US5863717A	US	3-11-1989	19990126	Abbott Laboratories & Lancaster, Wayne D. & Gregoire, Lucie	LANCASTER WAYNE D [US]; GREGOIRE LUCIE [US]	US	Use of conserved oligonucleotide primers to amplify human papillomavirus DNA sequences
7	Granted	In force	EP425995B1	DE	24-10-1990	19980304	Abbott Laboratories	LANCASTER WAYNE D [US]; GREGOIRE LUCIE [US]	US	Use of conserved oligonucleotide primers to amplify human papillomavirus DNA sequences
8	Filed	The application is deemed to be withdrawn	WO1991003718A1	DE GB NL	31-8-1990	19910321	Digene Diagnostics, Inc.	HIGGS, Thomas, W. TAUB, Floyd, E.	US	A highly sensitive method for detecting peroxidase

8	Granted	In force	US5116734A	US	25-10-1991	19920526	Digene Diagnostics, Inc.		HIGGS THOMAS W [US] ; TAUB FLOYD E [US]	US	Highly sensitive method for detecting peroxidase
9	Granted	In force	EP517704B1	DE GB NL	18-1-1991	19960508	Stichting Researchfonds Pathologie		MEIJER CHRISTOPHORUS JOANNES L [NL]; VAN DEN BRULE ADRIANUS JOHANNE [NL]; WALBOOMERS JAN MARCUS MARIA [NL]; SNIJDERS PETRUS JOSEPHUS FERDI [NL]	NL	Primers and process for detecting human papillomavirus genotypes by pcr
9	Granted	In force	US5364758A	US	16-7-1992	19941115	Stichting Researchfonds Pathologie & Meijer, Christophorus J.L.M. & Van Den Brule, Adrianus J.C. & Walboomers, Jan M.		MEIJER CHRISTOPHORUS J [NL]; VAN DEN BRULE ADRIANUS J [NL]; WALBOOMERS JAN M [NL]; SNIJDERS PETRUS J [NL]	NL	Primers and process for detecting human papillomavirus genotypes by PCR

10	Granted	In force	EP486661B1	DE GB NL	11-6-1991	19960207	Bio Merieux, Société ano-nyme		CROS PHI-LIPPE [FR] ; ALLIBERT PATRICE [FR] (+3)	FR	Method for detecting a nucleotide sequence by sandwich hybridization
11	Granted	Lapsed	EP507904B1	DE GB NL	25-10-1991	19990120	ORION YHTYMAE OY [FI]	SANGTEC	KALLIO ARJA [FI]; JALAVA TARJA [FI]	SE	Method for evaluating the adequacy of clinical specimens for hybridiza-tion assays and kit for performing the evalua-tion
12	Granted	Expired	US5346811A	US	15-1-1992	19940913	Cerveceria Po-lar|Universid ad Central de Venezuela		GALINDO-CASTRO IVAN [VE]; RAMIREZ JOSE L [VE] (+1)	US, VE	Method and products for human papil-lomavirus detection
13	Filed	The applica-tion is deemed to be withdrawn	WO1992014 847A2	DE GB NL	12-2-1992	19920903	Orgenics International Holdings B.V.		NUR, Israel PAPER, Thierry HERZBERG, Max	NL	Detection of high risk and low risk hu-man papillo-mavirus by enzymatic amplification of dna

14	Granted	In force	US5411857*	US	16-7-1992	2-5-1995	Institut Nationale de la Sante, Paris (FR) Institut Pasteur, Paris (FR)	ROCHE MOLECULAR SYSTEMS, INC., CALIFORNIA	BEAUDENON SYLVIE [FR]; KREMSDORF DINA [FR]; CROISSANT ODILE [FR]; ORTH GERARD [FR]	US	Probes for papillomaviruses and an in vitro diagnostic procedure for papilloma infections
14	Granted	Expired	EP0192001*	DE GB NL	1985-11-29	1992-03-11	PASTEUR INSTITUT [FR]; INST NAT SANTE RECH MED [FR]	F. HOFFMANN-LA ROCHE LTD.	ORTH GERARD; FAVRE MICHEL; KREMSDORF DINA; CROISSANT ODILE; PEHAUARNAUDET GERARD; BEAUDENON SYLVIE	Switzerland	Papilloma virus probes and in vitro methods for the diagnosis of papilloma virus infections
14	Granted	Expired	EP0235004*	DE GB NL	1987-01-30	1993-06-30	PASTEUR INSTITUT [FR]; INST NAT SANTE RECH MED [FR]	F. HOFFMANN-LA ROCHE LTD.	KREMSDOFDINA; CROISSANT ODILE; ORTH GERARD	Switzerland	Papilloma virus probes and in vitro methods for the diagnosis of Papilloma virus infections.

15	Granted	In force	EP0342128*	DE GB NL	1989-05-12	1995-04-26	PASTEUR INSTITUT [FR]	F. HOFFMANN-LA ROCHE LTD.	ORTH GERARD [FR]; FAVRE MICHEL [FR]; KREMSDORF DINA [FR]; PEHAU-ARNAUDET GERARD [FR]	Switzerland	Papillomavirus probes (HPV49, HPV50, HPV54, HPV55), products genetically and immunologically related to this papillomavirus and in vitro methods for the diagnosis of papillomavirus infections and for the production of antibodies against these papillomaviruses
15	Granted	In force	US5342930*	US	25-9-1992	30-8-1994	Institut Pasteur (FR)	ROCHE MOLECULAR SYSTEMS, INC., CALIFORNIA	ORTH GERARD [FR]; FAVRE MICHEL [FR]; KREMSDORF DINA [FR]; PEHAU-ARNAUDET GERARD [FR]	US	Isolated DNA of human papillomavirus type 54(HPV54)

15	Granted	In force	US5534439*	US	10-5-1994	9-7-1996	PASTEUR INSTITUT [FR]	ROCHE MOLECULAR SYSTEMS, INC., CALIFORNIA	Gerard Orth (FR) (+3)	US	Isolated DNA of human papillomavirus type 55 (HPV55)
15	Granted	In force	US5591574*	US	10-5-1994	9-7-1996	PASTEUR INSTITUT [FR]	ROCHE MOLECULAR SYSTEMS, INC., CALIFORNIA	ORTH GERARD [FR]; FAVRE MICHEL [FR]; KREMSDORF DINA [FR]; PEHAUARNAUDET GERARD [FR]	US	Probes, diagnostic method and immunization method based on papillomavirus types HPV 49 and HPV 50
16	Granted	In force	EP667918B1	DE GB NL	12-11-1992	20000216	Digene Diagnostics, Inc.		CHALLBERG SHARON [US] ; LORINCZ ATTILA [US] (+3)	US	Non-radioactive hybridization assay and kit

17	Granted	In force	EP0563255*	DE GB NL	1991-12-20	1994-09-28	PASTEUR INSTITUT [FR]; INST NAT SANTE RECH MED [FR]	F. HOFFMANN-LA ROCHE LTD	ORTH GERARD [FR]; VOLPERS CHRISTOPH [DE]; STREECK ROLF E [DE]	Switzerland	HPV39 PAPILLOMAVIRUS GENOME-DERIVED DNA SEQUENCES, THEIR APPLICATION TO IN VITRO DIAGNOSIS AND PRODUCTION OF IMMUNOGENIC COMPOSITIONS
17	Granted	In force	US5656423*	US	16-11-1993	12-8-1997	PASTEUR INSTITUT [FR]; INST NAT SANTE RECH MED [FR]	ROCHE MOLECULAR SYSTEMS, INC., CALIFORNIA	ORTH GERARD [FR]; VOLPERS CHRISTOPH [DE]; STREECK ROLF E [DE]	US	DNA sequences derived from the genome of the papillomavirus HPV39, their use in in vitro diagnosis and for the production of an immunogenic composition

17	Granted	In force	US5665535*	US	6-6-1995	9-9-1997	INST NAT SANTE RECH MED [FR]; PASTEUR INSTITUT [FR]	ROCHE MOLECULAR SYSTEMS, INC., CALIFORNIA	ORTH GERARD [FR]; VOLPERS CHRISTOPH [DE]; STREECK ROLF E [DE]	US	Polypeptides encoded by DNA sequences derived from the genome of the papillomavirus HPV39, antibodies thereto, and their use in in vitro diagnosis
18	Granted	Expired	US5382509A	US	23-11-1993	19950117	Behringwerke Aktiengesellschaft		GRIMMEL MARGITTA [DE]; DE VILLIERS ETHEL-MICHELE [DE]	DE	Method and kit for the diagnosis of human papillomavirus type 41
19	Granted	In force	US6228578B1	US	18-1-1994	20010508	Digene Corporation		IMPRAIM CHAKA [US]; CHALLBERG SHARON [US] (+2)	US	Non-radioactive hybridization assay and kit

19	Filed	Abandoned -- Failure to Respond to an Office Action	US20020012936A1	US	7-5-2001	20020131	{n/a}		LORINCZ, Attila (US) CHALL-BERG, Sharon (US) CULLEN, Allison (US) IMPRAIM, Chaka (US) LAZAR, James G. (US)		Non-radioactive hybridization assay and kit
20	Granted	In force	US5824488A	US	28-4-1994	19981020	The United States of America as represented by the De-parmtent of Health and Human Ser-vices & Rhim, Johng S.		WEBBER MUKTA M [US]; RHIM JOHNG S [US]	US	Immortalized and malig-nant human prostatic cell lines

20	Filed	PCT App. Not Ent. Europ. Phase	WO1995029990A1	DE GB NL	24-4-1995	19951109	Michigan State University|The Government Of The United States Of America, Represented By The Secretary, Department Of Health And Human Services		WEBBER, Mukta, M. RHIM, Johng, S.	US	Immortalized and malignant human prostatic cell lines
20	Granted	In force	US6255058B1	US	14-10-1998	20010703	Board of Trustees operating Michigan State University|The United States of America as represented by the Department of Health and Human Services		WEBBER MUKTA M [US]; RHIM JOHNG S [US]	US	Immortalized and malignant human prostatic cell lines
21	Filed	EP Withdrawn on 20.01.1997	WO1994026934A2	DE GB NL US	6-5-1994	19941124	Baxter Diagnostics Inc., US		BROWN, Janice	US	Human papillomavirus detection assay

22	Granted	In force	US5871902A	US	9-12-1994	19990216	The Gene Pool, Inc. & Weininger, Susan & Weininger, Arthur M.	WEININGER SUSAN [US]; WEININGER ARTHUR M [US]	US	Sequence-specific detection of nucleic acid hybrids using a DNA-binding molecule or assembly capable of discriminating perfect hybrids from non-perfect hybrids
22	Filed	Publication of search report published on 23/01/2008	EP1820864A2	DE GB NL	7-12-1995	20070822	The Gene Pool, Inc.	WEININGER SUSAN [US]; WEININGER ARTHUR M [US]	US	Method of detection of nucleic acids with a specific sequence composition
22	Filed	Abandoned -- Failure to Respond to an Office Action	US20030104361A1	US	29-9-1997	20030605	{n/a}	WEININGER SUSAN [US]; WEININGER ARTHUR M [US]		Method of detection of nucleic acids with a specific sequence composition

23	Filed	Examination is in progress	EP1327683A2	DE GB NL	15-5-1995	20030716	The Government of the United States of America, as, represented by the Secretary Department of Health, and Human Services|Northern Illinois University	HAMPEL ARNOLD [US]; DIPAOLO JOSEPH [US]; SIWKOWSKI ANDREW [US]	US	Human papilloma virus inhibition by a hairpin ribozyme

23	Granted	In force	EP759992B1	DE GB NL	15-5-1995	20041027	The Government Of The United States Of America, As, Represented By The Secretary, Department Of Health, And Human Services|The Board Of Regents For Northern Illinois, University	HAMPEL ARNOLD [US]; DIPAOLO JOSEPH [US]; SIWKOWSKI ANDREW [US]	US	Human papilloma virus inhibition by a hairpin ribozyme

24	Granted	In force	EP0433396*	DE GB NL	1989-08-29	1996-05-15	CETUS CORP [US]	F. HOFF-MANN-LA ROCHE AG	MANOS M MICHELE [US]; WRIGHT DEANN K [US]; TING YI [US]; BROKER THOMAS R [US]; WOLINSKY STEVEN M [US]	Switzerland	DETECTION OF HUMAN PAPILLO-MAVIRUS BY THE POLY-MERASE CHAIN RE-ACTION
24	Granted	In force	US5705627*	US	26-5-1995	6-1-1998	ROCHE MOLECU-LAR SYS-TEMS INC [US]	HOFFMANN-LA ROCHE INC.	MANOS M MICHELE [US]; BAUER HEIDI M [US]; GREER CATHERINE E [US]; RESNICK ROBERT M [US]; TING YI [US]	US	Detection of human papil-lomavirus by the poly-merase chain reaction us-ing specific L1, and E6 probes

24	Granted	In force	US5639871*	US	1-6-1995	17-6-1997	Roche Molecular Systems	HOFFMANN-LA ROCHE INC.	BAUER HEIDI M [US]; GRAVITT PATTI E [US]; GREER CATHERINE E [US]; IMPRAIM CHAKA C [US]; MANOS M MICHELE [US]; RESNICK ROBERT M [US]; ZHANG TRACY YI [US]	US	Detection of human papillomavirus by the polymerase chain reaction
25	Granted	In force	EP832214B1	DE GB NL	4-6-1996	20001227	Hybridon, Inc.		FRANK BRUCE L [US]; GOODCHILD JOHN [US] (+6)	US	Oligonucleotides specific for human papillomavirus
25	Granted	In force	US6509149B2	US	6-6-1995	20030121	Hybridon, Inc.		ROBERTS PETER C [US] ; FRANK BRUCE L [US] (+7)	US	HPV-specific oligonucleotides

25	Filed	Abandoned -- Failure to Pay Issue Fee	US20030055240A1	US	1-5-2002	20030320	{n/a}	ROBERTS, Peter C., (+8)		HPV specific oligonucleo-tides
26	Granted	In force	US5888724A	US	7-6-1995	19990330	The Trustees Of Columbia University In The City Of New York & SILVERSTEIN SAUL J (US); LUNGU OCTAVIAN (US); WRIGHT THOMAS C (US); RICHART RALPH M (US)	SILVERSTEIN, Saul, J. (+3)	US	Detection of high onco-genic-risk papilloma virus in high grade cervi-cal lesions and cancers by a PCR/ELISA assay
26	Filed	RO Process-ing Com-pleted-Placed In Storage	WO1996025521A1	DE GB NL	16-2-1996	19960822	The Trustees Of Columbia University In The City Of New York	SILVERSTEIN, Saul, J. (+3)	US	Detection of high grade cervical le-sions and cancers by a pcr/elisa assay

27	Filed	The application is deemed to be withdrawn	EP795610A1	DE GB NL	13-3-1996	19970917	Becton, Dickinson and Company		KERSTENS H M J [NL]; PODDIGHE P J [NL]; HANSELAAR A G J M [NL]	US	In situ hybridization signal amplification based on biotinylated tyramine deposition
28	Granted	In force	US6852487B1	US	4-2-1997	20050208	CORNELL RES FOUNDATION INC [US]; UNIV LOUISIANA STATE [US]; UNIV MINNESOTA [US]	Board of Supervisors of Louisiana State University	BARANY FRANCIS [US]; BARANY GEORGE [US] (+4)	US	Detection of nucleic acid sequence differences using the ligase detection reaction with addressable arrays
28	Filed	Response to Non-Final Office Action Entered and Forwarded to Examiner	US20030022182A1	US	26-9-2001	20030130	{n/a}		BARANY, Francis (US) BARANY, George (US) HAMMER, Robert P. (US) KEMPE, Maria (SE) BLOK, Herman (NL) ZIRVI, Monib (US)		Detection of nucleic acid sequence differences using the ligase detection reaction with addressable arrays

29	Granted	In force	US5981173A	US	11-2-1997	19991109	PASTEUR INSTITUT [FR]; INST NAT SANTE RECH MED [FR]	Roche Molecular Systems, Inc.	ORTH GERARD [FR] ; BEAUDENON SYLVIE [US] (+1)	US	Genital human papillomavirus type 68a (HPV-68a), related to the potentially oncogenic HPV-39
30	Filed	PCT - International Search Report Mailed to IB	WO1997035589A1	DE GB NL US	14-3-1997	19971002	Kopreski, Michael		KOPRESKI, Michael	US	Method enabling use of extracellular rna extracted from plasma or serum to detect, monitor or evaluate cancer

31	Granted	In force	US6277570B1	US	4-9-1998	20010821	NAXCOR [US]	Thien, Douglas	WOOD MICHAEL L [US]; ALBAGLI DAVID [US] (+4)	US	Nucleic acid sequence detection employing probes comprising non-nucleosidic coumarin derivatives as polynucleotide-crosslinking agents
31	Granted	In force	US6495676B1	US	3-9-1999	20021217	NAXCOR [US]	Thien, Douglas	WOOD MICHAEL L [US]; ALBAGLI DAVID [US] (+4)	US	Nucleic acid sequence detection employing probes comprising non-nucleosidic coumarin derivatives as polynucleotide-crosslinking agents

31	Granted	Expired Due to NonPayment of Maintenance Fees Under 37 CFR 1.362	US6737239B2	US	15-10-2002	20040518	WOOD MICHAEL L ; ALBAGLI DAVID (+5)	Thien, Douglas	WOOD MICHAEL L [US]; ALBAGLI DAVID [US] (+4)	US	Nucleic acid sequence detection employing probes comprising non-nucleosidic coumarin derivatives as polynucleotide-crosslinking agents
32	Granted	In force	US6063578A	US	22-10-1998	20000516	Signal Pharmaceuticals, Inc.		BARBOSA MIGUEL [US]; BILTER GRAHAM K [US]; KOVELMAN ROBERT [US]	US	Dual reporter system and methods of use therefore
33	Filed	PCT - International Search Report Mailed to IB	WO1999036578A1	DE GB NL	14-1-1999	19990722	Lakowicz, Joseph, R.		LAKOWICZ, Joseph, R.	US	Method and composition for detecting the presence of a nucleic acid sequence in a sample

34	Filed	PCT - International Search Report Mailed to IB	WO1999063118A1	DE GB NL US	27-5-1999	19991209	Visible Genetics Inc.	MAHONY, James SEADLER, Alan KIERSTEAD, Timothy CHONG, Sylvia	US	Method, reagent and kit for genotyping of human papillomavirus
34	Granted	In force	EP1082466B1	DE GB	27-5-1999	20060906	Bayer HealthCare LLC	MAHONY JAMES [CA]; SEADLER ALAN [US] (+2)	DE	Method, reagent and kit for genotyping of human papillomavirus
35	Granted	In force	US6489105B1	US	1-3-2000	20021203	McGill University|Imperial Cancer Research Technology|International Center for Genetic Engineering and Biotechnology	MATLASHEWSKI GREG J [CA]; BANKS LAWRENCE [IT] (+1)	CA, GB, IT	Screening method for determining individuals at risk of developing diseases associated with different polymorphic forms of wildtype P53
36	Granted	In force	US6420106B1	US	7-6-2000	20020716	Quantovir AB	GYLLENSTEN ULF [SE]; JOSEFSSON AGNETHA [SE]; MAGNUSSON PATRIK [SE]	SE	Method and kit for early cancer prediction

37	Granted	In force	US6495361B1	US	21-7-2000	20021217	University of Arkansas		HERMONAT, Paul, L. (US) LIU, Yong (US/CN)	US	Method of producing infectious papillomavirus in placental cells
37	Filed	RO Processing Completed-Placed In Storage	WO2002008264A2	DE GB NL US	23-7-2001	20020131	Board Of Trustees Of The University Of Arkansas|Hermonat, Paul, L.|Liu, Yong		HERMONAT, Paul, L. (US) LIU, Yong (US/CN)	US	Papillomavirus infected epithelial cells and methods of producing infectious papillomavirus in epithelial cells and uses thereof
37	Filed	RO Processing Completed-Placed In Storage	US20030157692A1	US	16-12-2002	20030821	University of Arkansas		HERMONAT, Paul, L. (US) LIU, Yong (US/CN)	US	Papillomavirus infected epithelial cells and methods of producing infectious papillomavirus in epithelial cells and uses thereof

38	Granted	In force	US6511805B1	US	31-8-2000	20030128	The Penn State Research Foundation		GOCKE CHRISTOPHER D [US]; CHRISTENSEN NEIL [US]	US	Methods for detecting papillomavirus DNA in blood plasma and serum
38	Filed	RO Processing Completed-Placed In Storage	WO2002018651A2	DE GB NL US	28-8-2001	20020307	The Pennsylvania State Research Foundation|Gocke, Christopher, D.|Christensen, Neil		GOCKE, Christopher, D. (US) CHRISTENSEN, Neil (US)	US	Methods for detecting papillomavirus dna in blood plasma and serum
38	Granted	In force	US7183053B2	US	24-12-2002	20070227	The Penn State Research Foundation		GOCKE CHRISTOPHER D [US]; CHRISTENSEN NEIL [US]	US	Methods for detecting papillomavirus DNA in blood plasma and serum
39	Filed	Examination is in progress	EP2000971860	DE GB NL	26-10-2000	20021211	Biomedlab Corp (KR)		ARK TAESHIN [KR]; PARK MISUN [KR]; KIM JEONGMI [KR]	KR	Genotyping kit for diagnosis of human papillomavirus infection
39	Filed	EPO Withdrawn on 07.11.2006	WO2003027323A1	DE GB NL US	18-9-2001	20030403	Biomedlab Co., Ltd.		YOON, Sung-Wook (+3)	KR	Genotyping kit for diagnosis of human papilloma virus infection

39	Granted	In force	US7301015B2		US	18-9-2001	20071127	Yoon, Sung-Wook, Seoul (KR) Park, Tae-Shin, Seoul (KR) Kim, Jeong-Mi, Seoul (KR) Park, Mi-Sun, Busan (KR)	YOON, Sung-Wook (+3)	KR	Genotyping kit for diagnosis of human papilloma virus infection
40	Filed	Notice of Allowance Mailed -- Application Received in Office of Publications	US20050142543A1		US	4-4-2001	20050630	{n/a}	BARANY, Francis (+4)		Method of designing addressable array for detection of nucleic acid sequence differences using ligase detection reaction
40	Filed	Examination is in progress	EP2001969050		DE GB NL	4-4-2001	20011025	Cornell Research Foundation, Inc.|Barany, Francis|Zirvi, Monib|Gerry, Norman, P.|Favis, Reyna|Klima n, Richard	BARANY FRANCIS [US]; ZIRVI MONIB [US]; GERRY NORMAN P [US]; FAVIS REYNA [US]; KLIMAN RICHARD [US]	US	Method of designing addressable array for detection of nucleic acid sequence differences using ligase detection reaction
41	Granted	In force	EP1309342B1	DE GB NL		3-7-2001	20061122	Merck & Co., Inc.	LOWE ROBERT S [US]; MEYERS CRAIG M [US]; ZHANG JIAPING [US]; KAUPAS MICHELLE	US	Production of a chimeric human papillomavirus

									[US]; JANSEN KATHRIN U [US]		
41	Granted	In force	US6841157B2	US	28-7-2003	20050111	LOWE ROBERT S; MEYERS CRAIG M (+4)	Merck & Co., Inc.	LOWE ROBERT S [US]; MEYERS CRAIG M [US] (+3)	US	Production of chimeric human papil-lomavirus
42	Filed	Abandoned -- Failure to Respond to an Office Action	US20030148284A1	US	17-12-2001	20030807	Vision, Todd J. (US) (+5)		VISION, Todd J. (+5)	US	Solid phase detection of nucleic acid molecules
43	Filed	Abandoned -- Failure to Respond to an Office Action	US20030059806A1	US	3-6-2002	20030327	Science & Technology Corporation @ UNM		WHEELER, Cossette (US) GOODALL, Cheri (US)	US	Probes for the detection of human papillomavi-rus
44	Filed	Entry into national phase	WO2002103050A2	DE GB NL US	13-6-2002	20021227	University Of Wales Col-lege Of Medi-cine|Hart, Keith, William		HART, Keith, William	GB	Virus detec-tion method, primers therefor and screening kit

44	Filed	The application is deemed to be withdrawn	EP1409730	DE GB NL	13-6-2002	20021227	University Of Wales College Of Medicine|Hart, Keith, William	HART KEITH WILLIAM [GB]	GB	Virus detection method, primers therefor and screening kit
44	Filed	Application Returned back to Pre-exam	US20060575 61	US	13-6-2002	20021227	University Of Wales College Of Medicine|Hart, Keith, William	HART KEITH WILLIAM [GB]	GB	Virus detection method, primers therefor and screening kit
45	Filed	Abandoned -- Failure to Respond to an Office Action	US20050175 987A1	US	19-8-2002	20050811	Jansen, Kathrin (US) (+3)	JANSEN, Kathrin (US) (+3)	US	Fluorescent multiplex hpv pcr assays using multiple fluorophores
45	Granted	In force	EP1421200B 1	DE GB NL	19-8-2002	20061213	Merck & Co., Inc.	JANSEN KATHRIN U [US] ; TADDEO FRANK J [US] (+2)	US	Fluorescent multiplex hpv pcr assays using multiple fluorophores

46	Filed	EP With-drawn on 09.11.2006 and US Abandoned -- Failure to Respond to an Office Action	WO2003057927A2	DE GB NL US	7-1-2003	20030717	Norchip A/S|Allard, Susan, Joyce|Karlsen, Frank	KARLSEN, Frank (NO)	NO	Detection of human papil-lomavirus e6 mrna
46	Filed	Non Final Action Mailed	US20050118568A1	US	7-1-2003	20050602	{n/a}	KARLSEN, Frank (NO)		Method for detecting human papil-lomavirus mrna
46	Filed	Abandoned -- Failure to Respond to an Office Action	US20050244813A1	US	7-1-2003	20051103	{n/a}	KARLSEN, Frank (NO)		Detection of human papil-lomavirus e6 mrna
46	Filed	Examination is in progress	EP1715062A2	DE GB NL	7-1-2003	20061025	Norchip A/S	KARLSEN FRANK [NO]	NO	Method for detecting human papil-lomavirus mrna
46	Granted	In force	EP1463839B1	DE GB NL	7-1-2003	20070221	Norchip A/S	KARLSEN FRANK [NO]	NO	Method for detecting human papil-lomavirus mrna
46	Filed	Docketed New Case - Ready for Examination	US20070292841A1	US	28-2-2005	20071220	Norchip A/S	KARLSEN FRANK [NO]	NO	Detection of Human Papil-lomavirus

47	Filed	Notice of Appeal Filed	US20040157220A1	US	10-2-2003	20040812	Kurnool, Purnimal (US) (+2)		KURNOOL, Purnima	US	Methods and apparatus for sample tracking
48	Granted	In force	EP1504127B1	DE GB NL	10-3-2003	20060830	GenoID KFT		TAKACS TIBOR [HU]; JENEY CSABA [HU]	HU	Amplification-hybridisation method for detecting and typing human papillomavirus
48	Granted	In force	US7294488B2	US	10-3-2003	20071113	Genoid KFT		ENEY CSABA [HU]; TAKACS TIBOR [HU]	HU	Amplification-hybridisation method for detecting and typing human papillomavirus
49	Filed	Final Rejection Mailed	US20040203004A1	US	10-4-2003	20041014	Bernard, Hans Ulrich, (US) (+2)		BERNARD, Hans Ulrich (+2)	US, SG	Diagnostic apparatus and method
49	Filed	The application is deemed to be withdrawn	WO2004090166A1	DE GB NL US	25-3-2004	20041021	Institute Of Cell And Molecular Biology		BERNARD, Hans Ulrich (+2)	SG	A method and a kit for diagnosing cervical cancer

50	Filed	Non Final Action Mailed	US20050202436A1	US	17-7-2003	20050915	{n/a}	GHARIZADEH, Baback	{n/a}	Target-specific multiple sequencing primer pool for microbial typing and sequencing applications in DNA-sequencing technologies
51	Filed	The application is deemed to be withdrawn	WO2004018711A2	DE GB NL US	20-8-2003	20040304	University College London|Ming-Qing, Du	MING-QING, Du	GB	Diagnostic test
52	Filed	Examination is in progress	WO2004031416A1	DE GB NL US	1-10-2003	20040415	Quantovir Ab	GYLLENSTEN, Ulf MOBERG, Martin	SE	Method and kit for quantitative and qualitative determination of human papillomavirus
52	Filed	Non Final Action Mailed	US20070037137A1	US	1-10-2003	20070215	Quantovir Ab	GYLLENSTEN, Ulf MOBERG, Martin	SE	Method and kit for quantitative and qualitative determination of human papillomavirus

53	Granted	In force	US7063963B2	US	22-10-2003	20060620	COLE STEWART; STREECK ROLF E; ROCHE MOLECULAR SYSTEMS, INC	Roche Molecular Systems, Inc.	COLE STEWART [FR]; STREECK ROLF E [FR]	US	Determined DNA sequences derived from a papillomavirus genome, their uses for in vitro diagnostic purposes and the production of antigenic compositions
54	Filed	Abandoned -- Failure to Respond to an Office Action	US20040248085A1	US	24-11-2003	20041209	Lee, Sang-Wha, Yongin-si (KR) (+5)		LEE, Sang-Wha	KR	General primers and process for detecting diverse genotypes of human papillomavirus by PCR
54	Filed	The application is deemed to be withdrawn	WO2004050917A1	DE GB NL	28-11-2003	20040617	Albiomed Co., Ltd.	LEE, Sang-Hwa (+5)		KR	General primers and process for detecting diverse genotypes of human papillomavirus by pcr

55	Filed	Non Final Action Mailed	WO2004059277A2	US	24-12-2003	20040715	Tong, Sun-Wing|Chan, Olivia, Wai-Hin|Chow, Tat-Chong|Yu, Vivian	CHAN, Olivia, Wai-Hin (+2)	CN	Methods of collecting and transporting vaginal discharge for detection of infectious organisms and to facilitate cervical cancer screening
55	Filed	Non Final Action Mailed	US20060166333A1	US	24-12-2003	20060727	Tong, Sun-Wing (CN) (+3)	TONG, Sun-Wing (+3)	CN	Methods of collecting and transporting vaginal discharge for detection of infectious organisms and to facilitate cervical cancer screening

56	Filed	Examination is in progress	WO2004083455A1	DE GB US	19-3-2004	20040930	The Murdoch Childrens Research Institute|Melbourne Health|South Eastern Sydney Area Health Service		VISVANATHAN, Kumar (+2)	AU	Therapeutic, prophylactic and diagnostic agents
56	Filed	Docketed New Case - Ready for Examination	US20070128586A1	US	19-3-2004	20070607	VisvanathaN, Kumar (AU) (+2)		VISVANATHAN, Kumar (+2)	AU	Therapeutic, prophylactic and diagnostic agents
57	Granted	In force	EP1740951B1	DE GB NL	29-4-2004	20080305	Ramael, Marc		RAMAEL MARC [BE]	BE	Method and kit for detecting components in a sample
58	Filed	The application is deemed to be withdrawn	WO2005014634A1	DE GB NL US	12-8-2004	20050217	AGT Biosciences Limited		COLLIER, Gregory (+2)	AU	A gene and uses therefore
59	Filed	Abandoned -- Failure to Respond to an Office Action	US20050266417A1	US	10-9-2004	20051201	{n/a}		BARANY, Francis (+3)		Methods for identifying target nucleic acid molecules

60	Granted	In force	US7211391B2	US	15-11-2004	20070501	Institut Curie		SASTRE-GARAU, Xavier (FR) CARTIER, Isabelle (FR)	FR	Methods and compositions for predicting the outcome of cervical intra-epithelial neoplasia
61	Filed	Withdrawn Abandon-ment, await-ing examiner action	US20060029943A1	US	6-12-2004	20060209	Hermonat, Paul (US) (+2)		HERMONAT, Paul L. (+2)	US	Composi-tions, meth-ods and products comprising human papil-lomavirus for detecting and treating a cancer
62	Filed	Examination is in progress	WO2005078139A2	DE GB NL US	9-2-2005	20050825	Thomas Jefferson University		CROCE, Carlo, M. (+3)	US	Diagnosis and treat-ment of can-cers with microrna located in or near cancer-associated chromosomal features

62	Filed	Non Final Action Mailed	US20060105360A1	US	29-7-2005	20060518	{n/a}	CROCE, Carlo, M. (+3)	{n/a}	Diagnosis and treatment of cancers with microrna located in or near cancer associated chromosomal features
63	Filed	The application is deemed to be withdrawn	WO2005090608A2	DE GB NL US	4-3-2005	20050929	Advandx, Inc.	STENDER, Henrik [DK] FIANDACA, Mark [US]	US	High affinity probes for analysis of human papillomavirus expression
64	Filed	Docketed New Case - Ready for Examination	US20070248968A1	US	18-3-2005	20071025	Goodgene Inc.	MOON, Woo-Chul (+6)	US	Probe of Human Papillomavirus and Dna Chip Comprising the Same
65	Filed	Request for examination was made	WO2005121373A2	DE GB US	3-6-2005	20051222	Advandx, Inc.	FIANDACA, Mark (+2)	US	Hybridization of pna probes in alcohol solutions
65	Filed	Non Final Action Mailed	US20070128646A1	US	1-12-2006	20070607	{n/a}	FIANDACA, Mark (+2)		Hybridization of PNA probes in alcohol solutions

66	Filed	Request for examination was made	WO2006063065A2	DE GB NL US	8-12-2005	20060615	Gen Probe Incorporated	NORMAN, Sylvia, A. (US) (+3)	US	Detection of nucleic acids from multiple types of human papillomaviruses
66	Granted	In force	US7354719B2	US	8-12-2005	20080408	Gen-Probe Incorporated	NORMAN SYLVIA A [US]; BUNGO JENNIFER J [US] (+2)	US	Detection of nucleic acids from multiple types of human papillomaviruses
67	Filed	The application is deemed to be withdrawn	WO2006096727A2	DE GB US	7-3-2006	20060914	Cellay LLC	MOEN JR., Phillip T.	US	Methods for detecting integrated dna
68	Filed	The application is deemed to be withdrawn	WO2006098582A1	DE GB NL US	14-3-2006	20060921	Sungkyunkwan University	YANG, Joo-Sung [KR] CHA, Hyeran [KR]	KR	Primer for detection of human papillomavirus
69	Filed	The application has been published	WO2006116276A2	DE GB NL US	24-4-2006	20061102	Merck & Co., Inc.	TADDEO, Frank, J. (+3)	US	Real-time hpv pcr assays
70	Filed	Request for examination was made	WO2006116303A2	DE GB US	24-4-2006	20061102	Merck & Co., Inc.	TADDEO, Frank, J. (+3)	US	Fluorescent multiplex hpv pcr assays

71	Filed	The international publication has been made	WO2007082881A2	DE GB US	16-1-2007	20070726	Glaxosmithkline Biologicals S.A.|Delft Diagnostic Laboratory B.V.|Colau, Brigitte, Desiree, Alberte|Kleter, Gijsbertus, Everardus, Maria|Van Alewijk, Dirk, Cornelis, Jerrefaas, Gelde|Van Doorn, Leendert, Jan		COLAU, Brigitte (+3)	BE, NL	Assay and materials therefor
72	Filed	The international publication has been made	WO2007100198A1	DE GB US	23-2-2007	20070907	Ahn, Woong Shick|Han, Byoung-Don|Oh, Yong Taek|Chun, Sung-Min|Bae, Su Mi		AHN, Woong Shick (+4)	KR	Kits and method for detecting human papilloma virus with oligo nucleotide bead array

73	Filed	PCT - Docketed Chapter 1 Case	WO2007103558A2	DE GB US	9-3-2007	20070913	The Regents Of The University Of California|Reich, Norbert, O.|Braun, Gary|Estabrook, R., August	REICH, Norbert, O. (+2)	US	Hybrid energy transfer for nucleic acid detection
73	Filed	Docketed New Case - Ready for Examination	US20070238096A1	US	9-3-2007	20071011	The Regents of the University of California	REICH, Norbert, O. (+2)	US	Hybrid energy transfer for nucleic acid detection
74	Filed	The international publication has been made	WO2008017162A1	DE GB US	10-8-2007	20080214	Chu Sainte-Justine, Le Centre Hospitalier Universitaire Mere-Enfant|Brukner, Ivan|Labuda, Damian|Krajinovic, Maja	BRUKNER, Ivan (+3)	CA	Oligonucleotides for discriminating related nucleic acid sequences

N.B.
* Patents added in November 2008 by complementary search approach

V. Conclusion

5.1 Introduction

This report has examined the development and clinical use of three molecular diagnostics where intellectual property has been a key feature of the test's evolution. In WP2 we noted that there are three broad models of how a patent holder can exploit their biomarker IP. Each of these models has been examined in our three case studies:

- FVL – owner and exclusive licensee do not develop a test kit, but license the patent to others who do so
- TMPT - company in-licenses suite of IP to develop Laboratory Developed Tests (LDT) in the its own reference laboratory with the aim of creating a monopoly on patient access to the test (TPMT);
- HPV - company develops a test kit which is sold to multiple laboratories but prevents other kit manufacturers from entering the market.

This and other key features of these cases related to these conclusions are set out in Table 10.

Table 10: Summary of key features of the case studies

Genetic test (time developed)	Test modality	Key biomarker IP owner(s)	Biomarker patenting and licensing strategies	Exclusive licensee's commercialisation strategy	Test availability	Clinical use/ clinical validity
FVL (mid-1990s onwards)	Genetic test, and (less specific) phenotypic tests available.	European University	US/ EU patents, exclusive licence	Granting of multiple sub-licenses to kit developers (inc. FDA approved kits), large reference labs, weak enforcement	Widely offered - diversity of infringing kits and services are available	Widely used test, but weak evidence of utility, even after more than 12 years of use
TPMT (late 1990s onwards)	Genetic test, two kinds of phenotypic test and antibody test all available.	North American Hospitals, US biotech	US patents, less EU patent coverage. Key IP held by or exclusively licensed to biotech service provider	Laboratory developed testing service – strongly enforced with mixed success (US only to date)	Widely offered in the EU, more limited availability in USA, some infringement (services)	Widely used in some fields only. Evidence base and guidelines still developing
HPV (late 1980s onwards)	Genetic test compliments older, much less specific cytological test	US universities and companies / EU research institutes	Broad US and EU patent coverage. Several Exclusive licences	FDA-Kit developed, strongly enforced (in US only) with mixed success	Kit widely marketed in US and parts of EU, but some infringement (kits and services)	Widely used, except in UK (pending validation) but users want next generation products

A prominent feature of all three cases has been the exclusive licensing of biomarker IP by public sector organisations to small or medium-sized firms. These firms have exploited their IP in three completely different ways. In the case of FVL, a number of sub-licenses were granted, allowing in particular the development of several FDA-approved kits. In the case of TPMT, sub-licenses from one exclusive licensee were issued, but nonetheless a monopolistic testing service provider has emerged in the US, but has yet to enforce this position in the EU (and may have less IP coverage to do so). In the case of HPV, a monopolistic kit-provider has emerged in the US, but once again this monopoly position has not been as easily replicated in

the EU. There is also evidence of differential enforcement strategies in the case of test kits and LDTs in both FVL and HPV.

The case studies are important for their potential in demonstrating the complex ways in which biomarker IP interacts with other factors to affect the R&D process, clinical uptake and patient access to new tests as described in the following sections.

5.2 Types of IP, acquisition and exploitation

5.2.1 Thinking beyond the notion of broad, blocking gene patents

Patents on genes are just one form of IP relevant to genetic testing, and these case studies have shown that there may be significant limitations restricting how companies can exploit this IP, indicating that the biological context of the patented invention as well as the specific claims the patent holder has been awarded substantially influence a patent's likely commercial impact.

The cases provide evidence about the variety of types of patents which are available and have been sought, illustrating the range of biomarker-related IP in the IVD industry. Patents have been granted on nucleotide sequences, methods and kits and on phenotypic tests (enzymes and measurement of metabolites). It is important to note that the cases show genetic tests are not necessarily impossible to invent around. The initial patents have not always been obstructive. Mayo's patent on the wildtype TPMT gene for example has not apparently allowed them to offer the DNA test, which relies on the detection of certain mutations claimed in the patent held by St. Jude Children's Research Hospital. Digene/Qiagen have not been able to defend their HPV52 patent in litigation with Third Wave/Hologic, although some key IP did expire before it was tested in this case. Also, in all three cases the molecular diagnostic is not the sole means of clinical testing as phenotypic test methods are also possible. All the molecular tests we have examined have their shortcomings and clinicians may wish to access both types of test for the same patient. In the case of TPMT and FVL no one company has managed to monopolise all forms of testing.

The density of patenting has been seen to vary widely between the cases and appears to depend primarily on two factors: the biological basis of the test (e.g. whether a single mutation is tested or a gene containing many mutations, or whether many genes are involved) and the number of players in the market, which itself is probably related to expectations of potential market size. Thus HPV has the most patents because of the large number of different HPV types that occur and have been patented, and the variety of ways of identifying HPV, from hybrid capture to PCR based methods. The spur for companies to enter the space and develop new patentable methods are: firstly, the potential size of the HPV screening market; and, secondly, the emerging clinical demand for alternatives to the Digene/Qiagen test.

5.2.2 The role of public sector exclusive licences in diagnostic controversies

All three cases presented here involve patent holders in the private sector and the public sector and in each case much of the key IP has come from the public sector. This indicates that the issues arising from the acquisition and exploitation of biomarker IP are not attributable simply to the pursuit of competitive advantage between biotech firms. Rather it is universities and hospitals such as St. Jude, Georgetown, and Rijks Universteit Leiden who hold much of the most important IP and who help to set the terms for its exploitation through their choice of licensees and their frequent use of exclusive licences. However the granting of sub-licenses in two of the three cases indicates that an exclusive licensee selected by the university may not always choose to monopolise downstream revenues, although clearly in some cases this is a favoured strategy. Certainly it allows for more full monitisation of the IP, with the market able to put a premium on the value of companies owning this IP in a way that non-exclusive licensees are unlikely to see. This is illustrated by the size of the acquisition value of Digene.

The case of FVL illustrates that the nature of the contract between licensor and licensee may have a substantial impact on subsequent enforcement activity and that, as such, the granting of exclusive licenses per se may not be the root cause of diagnostic patent controversies such as those involving Myriad and Athena – see Cook-Deegan et al 2009. Rather it is suggested that exclusive licensing may be a legitimate way to place responsibility for broader licensing with an organisation better equipped to manage this task. However, clearly this is an area where there is considerable scope for best practice to be developed or better disseminated.

5.2.3 Enforcement of exclusivity for kit makers and LDT service providers[194]

Patents in genetic testing have not consistently provided monopolies for IP holders. In all three cases laboratories are infringing patents, and often are doing so without any apparent threat of enforcement by the IP holder. Furthermore this infringement has occurred even when the indications are the royalty payments are within a price range that the market can bear, as in the case of FVL. In seeking to understand the significance of this differential approach to enforcement, we must bear in mind that this is just one of a number of ways in which there is a lack of a level playing field for LDTs and kits. There are a number of factors which affect the ability of a laboratory to offer a test as an LDT and a manufacturer to develop a test kit, including cost, time and regulatory hurdles. It is cheaper and faster to produce an LDT and the regulatory requirements are often less onerous (a factor which, conversely, adds further costs and time to kit production). LDTs can be modified more easily allowing swifter adoption of incremental improvements (including new markers and new techniques). Crucially, the principal factor which deters the FDA from regulating LDTs in the USA is probably the same one which deters patent holders from enforcing their IP in labs – the sheer number of labs offering tests makes the task of enforcement far greater. Hundreds of labs might offer a particular test as an LDT, while the number of manufacturers producing kits is likely to remain in at most in low double digits (perhaps 10-15 as indicated by FVL).

In the US an alternative strategy for an IP holder would be to focus enforcement on the small number of major reference labs which dominate this national market. This would not only be more manageable in terms of number of companies to pursue, and more acceptable to those who do not wish to pursue labs in the public sector, but it would likely capture a very high proportion of the volume of tests carried out in the US. However, the challenge in this respect is the resources which such industry leaders have to devote to IP issues and their apparent willingness to enter into litigation. Also the large, well established, multi-product diagnostic companies may not want to sue their customers as this could damage other product markets (see remarks of reference lab executive in WP2).

Some kit manufacturers who had acquired licenses to produce Factor V Leiden tests complained about the failure to require labs to license their LDTs. From the perspective of the Myriad case and the concerns about how gene patents might impact public hospital labs ability to offer their own tests, the Factor V Leiden case illustrates the potential for a nuanced approach to IP exploitation that can address such sensitivities. However, there are a number of factors at work here, which may limit how far this can be generalised, including the fact that gene sequencing, which is central to the practice of BRCA testing, is not reducible to a low cost kit at present, preventing Myriad from exploiting its IP by focusing on kits. The second issue is that the Factor V Leiden market is large enough to make it attractive to a number of kit manufacturers, and that the test itself is relatively simple. Finally, the approach taken in all cases depends crucially on the motivations of the patent-holder and the licensee. For example in the case of Factor V Leiden the assignee had asked that the patent is not enforced against individual academic research institutions. In some cases the fragmentation of the market makes litigation against a given infringer less lightly to be profitable, given the high legal expenses involved in building a case and risk of losing. In other cases, for example Prometheus vs. Quest, reported here, smaller companies may be motivated to pursue en-

[194] We thank two legal experts for their observations summarised here.

forcement where the marginal revenue, or the precedent, is more valuable to their business than perhaps would be the case for an incumbent.

5.2.4 The role of market size and other regional factors

The BRCA case (described by Parthasarythy 2007 and others) was notable for the quite different outcomes that Myriad's strategy led to in the US and Europe (and indeed in Canada). In both the US and Europe there was professional opposition to Myriad's efforts to enforce its IP, but structural factors made it more difficult for Myriad to overcome that opposition in Europe. In the WP2 laboratory survey and industry interviews (see WP2 report) we have already confirmed that regional differences in approach to biomarker IP extend far beyond the Myriad case; the HPV and TPMT cases add further evidence of a regional divide, although there would appear to be little difference between Europe and the US in the case of Factor V Leiden, either in terms of the patent landscape or enforcement activities.

In the case of TPMT there are a number of key differences, including the fact that crucial IP is patented in the US but not in Europe. Prometheus, the company who hold the broadest IP rights, have been active in enforcing its position in the USA in order to secure a monopoly on testing for its own laboratory. In the US the availability of alternative tests has continued with laboratories attempting to challenge or invent around existing IP. Thus far it would appear that Prometheus has not attempted to prevent European labs from offering TPMT tests, although this is due to their continued ability to grow their US market and their strategic focus rather than of other reasons.

HPV has strong similarities to TPMT, in that the holder of key IP has actively pursued a US monopoly and there has been litigation with rival companies in the US but in Europe there is no evidence that the company is seeking to establish a monopoly although it has a dominant market position. Not only is there no public record of HPV litigation in Europe, there is a growing number of companies bringing tests to market. The presence of unlicensed kits in the EU and the US, launched in a climate where litigation must be a primary consideration for manufacturers indicates a strong financial incentive for risk taking in these entrants, and perhaps is an indication of weaknesses in the IP or competitive position of the IP owner. In either case this again reaffirms arguments in the previous section that the IP owner's monopolist position may be difficult to protect. In our WP2 report we suggested that the value of biomarker IP was still uncertain; these case studies have reinforced that perception.

5.3 Development and diffusion – the challenges of translation

There has been much policy discussion about the difficulties associated with translating genomic research discoveries into well-accepted and well-adopted clinical use. The case study which best illustrates these challenges is TPMT, Whilst there were potential negative impacts from the restriction of wide provision of TPMT testing by the IP holder, the most immediate barriers to clinical uptake are reimbursement arrangements and perceptions of a lack of clinical utility. Uptake of the test has clearly varied due to differences in evidence and guidelines across clinical fields which have left many clinicians unaware of the reasons for using the test.

These factors were also of crucial importance in the case of HPV, where uptake in the UK is awaiting evidence from the UK trials established to assist the National Screening Committee in deciding whether the test has a role in the existing Cervical Screening programme, but where positive coverage decisions in the USA flowed quickly from FDA approval of the Digene kit and its use in the pivotal ALTS trial whose findings formed the basis for clinical guidelines recommending use of the test. The role of guidelines in driving uptake in Germany and the Netherlands is less clear but the development of guidelines in these countries stands in contrast to the situation in the UK.

Conversely Factor V Leiden has enjoyed widespread and rapid adoption despite subsequent challenges to its clinical utility, owing to the simple nature of the test and its novelty in the field at the time of introduction.

The role of biomarker IP in the process of development and diffusion of testing therefore has varied between cases, but it is reasonable to suggest that in all three cases other factors have played a more important role.

To what extent do our cases suggest that development of a robust evidence base to guide use of the test and drive clinical uptake can be encouraged by companies holding biomarker IP?

In the case of HPV, Digene would appear to have played a significant role in the development of the evidence base, funding a number of studies such as the UK HART trial. However, many HPV studies like the ALTS trial were publicly funded, albeit with the company providing support in the form of cheap or free assays. In the case of TPMT Prometheus claimed that they supported studies by academic research groups. In the case of Factor V Leiden, the patent assignee has played an ongoing role in research to identify new markers and elucidate the clinical significance of the gene (but it would appear that the licensee has added little or no value in this respect, other than allowing a range of other tests to become available by not enforcing their monopoly). The continued role of the assignee, suggests the potential for patent royalties to stimulate research, since these monies have provide an additional source of funding for research. However, in TPMT and FVL there are questions that remain over clinical utility, suggesting that the biomarker IP may not be sufficiently powerful an incentive to invest in addressing all the evidence gaps. In particular it appears that health providers have a propensity to encourage or even require local studies of clinical utility or cost effectiveness which clearly involves the expenditure of significant resources in each territory, and indeed in each clinical application the test is to be used in. The organisation of these studies also may take some years. The cost and delay are both significant factors for diagnostic firms, especially those that do not have large resources to invest. One strategy to address this issue is to ensure that the clinical need which one's test is seeking to address is sufficiently compelling that public funding is likely to support postmarket studies, as has been the case with the HPV test.

On its own a solid evidence base may not be sufficient to ensure broad and swift uptake; it may also be necessary to build awareness of that evidence base. This may be achieved through a variety of mechanisms such as the promotion of clinical guidelines by professional bodies, but companies may play the key role if they make a significant investment in sales and marketing activities. Prometheus and Digene/Qiagen have each used their own sales force to target doctors to generate demand for the test. In the case of Digene this is an unusual departure, since kit manufacturers do not generally promote direct to physicians, preferring instead to target laboratories who will then in turn promote the test to doctors. The more radical aspect of Digene's approach has been the adoption of direct-to-consumer promotion, although this is a broader trend in the medical devices industry.

However, opinions about such marketing are mixed with some suggesting that companies may want to get to market too quickly (i.e. before they have sufficient robust evidence to justify routine clinical use of a test) and may try to drive inappropriate utilisation (an accusation levelled at Digene by one of our US interviewees). One European interviewee described Digene as “very, very pushy”. However, there are a number of factors which the company might cite to suggest that their approach is well-justified, including: the strong support amongst HPV researchers and the pathology community for use of the Digene/Qiagen test; consensus that the HPV market is under-penetrated, in part due to clinician conservatism, and the longstanding problems increasing participation in even existing cytological screening programmes. Criticism of Digene/Qiagen provides a parallel with the BRCA/Myriad case where the use of DTC advertising has been met with some hostility. Both cases suggest that there may be some level of resistance to IVD companies adopting the more aggressive marketing strategies of the pharmaceutical industry. To the extent that such activities are predominantly carried out by companies with a strong patent position which offers them a market monopoly, then this provides another indication of how biomarker IP may be changing business models in the IVD industry and presenting novel challenges for policy makers.

5.4 IP and incremental innovation to improve quality

Concerns about DTC promotion are not the only aspect of changing business models which have raised concerns. Some have suggested (as in the TPMT case here) that monopoly provision of a testing service leads to problems when no verification of quality or accuracy is available (Cook-Deegan et al. 2009), although there are obvious counter-arguments also about the quality of 'homebrews' provided by smaller labs that may provide testing services when no monopoly exists. Some scholars argue that the adoption of biomarker IP is driving the IVD sector towards a pharma model of innovation that is now failing to deliver. As a recent Canadian report from the International Expert Group on Biotechnology, Innovation and Intellectual (IEGBII) argues:

> "The end of the Old IP era came much closer in view in 2007 when CEOs and senior managers of pharmaceutical companies stated that their business model of establishing high IP barriers around blockbuster drugs no longer worked."[195]

The report goes on to argue that the pharma industry's IP-based innovation model is linear and fails to capture the essentially cyclical and collaborative nature of innovation. One of the key criticisms of the Myriad BRCA patent was that by preventing multiple labs from performing testing Myriad would block incremental innovation, in terms of both the development of new testing methods and the identification of new mutations. In this study the case which most reinforces this concern is HPV where the Digene test has well-established limitations and where there is strong demand for alternative tests to address these problems, but where the entry of new tests to the market has been delayed in part by Digene's patent litigation. It should be noted that research use of other tests such as Roche's Linear Array kit has not been prevented, even in the US, and that IP is not the only reason for the lack of competition, as our US interviewees indicated they thought that the need for FDA approval was also a factor. Furthermore, the patent litigation has not stopped companies such as Third Wave and Ventana selling HPV ASRs enabling labs to create their own LDTs and nor is there any evidence of patent litigation to block the use of HPV LDTs. Nevertheless, the HPV market appears to be one where laboratories would in general appear to prefer to wait for an FDA-approved kit and where IP has been a factor hindering incremental innovation by multiple players. Any evaluation of the harm that may have arisen from this lack of open, competitive innovation must be balanced against the benefits that have accrued from the presence of a single company committed to playing a key role in the development of the clinical evidence base for HPV testing.

Incremental innovation in Factor V Leiden testing is more open because there is a greater tendency for labs to develop homebrews and therefore less reliance on FDA-approved kits. When coupled with the lack of IP enforcement and the relatively large size of the Factor V market (compared with other heritable markers) this has created a fertile environment for incremental innovation by both labs and kit makers – although as noted above the clinical utility of the test is still uncertain. The HPV and Factor V Leiden cases illustrate the very different outcomes which can arise from strong biomarker patents and the crucial role played by licensing strategies in determining the potential for incremental innovation by multiple players.

5.5 Limitations of this study and implications for future policy and research

This report covers the results of a relatively small-scale enquiry into three cases studies of particular genetic tests that have been important tests in their class, and as such does not address the development and commercialisation of all tests within a class of test. Furthermore, the scale of fieldwork undertaken must be regarded as exploratory. Absence of evidence should not therefore be assumed to be evidence of absence.

Furthermore there are many missing details in the cases reported here due to difficulties in finding data. The authors of the report note that information on patenting and licensing activi-

[195] The International Expert Group on Biotechnology, Innovation and Intellectual Property *Toward a new era in intellectual property: from confrontation to negotiation* (Montreal, Canada, 2008)

ties in the diagnostics sector is particularly difficult to find and to collate in a comprehensive manner. This is especially the case for European patent documents. This is surprising to us because it is a foundational principle that the patent system provides protection for inventors in return for disclosure of their inventions. However at the present time this information is much more difficult to search for in European databases than it is at the USPTO. In relation to our findings in WP2 based on the survey of EU-based clinical laboratories' awareness of patents, and results of similar enquiries in the FVL and TMPT cases in this report, it is our assessment that the current publicly available IT systems do not adequately support practitioners of patentable arts in avoiding infringement or in the search for potential licensors through identification of patent owners. Furthermore there is also no systematic way to identify licensors or licensees in the EU or the USA as parties are under no obligation to disclose this information.

The case studies presented here demonstrate that while the BRCA case offered policymakers an early indication of some of the issues that may arise from the growing importance of biomarker IP in the molecular diagnostics sector, a single case can at best provide only a partial understanding of the range of strategies for exploiting such IP and the variety of potential outcomes. It is hoped that these additional case studies create a fuller picture. Generalisation from these cases should be undertaken with care as it must be borne in mind that the sector is moving very rapidly and some of the greatest challenges in dealing with biomarker patent thickets (which clearly is what the HPV case may be called) may arise in applications not covered in these cases. A number of other case studies have been undertaken by other research groups in parallel to this study and a more comprehensive and robust analysis may be provided from combining these results, however this is beyond the scope of this present report.

As noted in our WP2 report, an increasing number of companies are developing polygenic tests for applications such as measuring heritable susceptibility to common diseases or molecular profiling of tumours for prognosis and treatment selection in post-operative cancer patients. Such applications have considerable potential for problems arising from royalty stacking and may make the need to develop coherent policies to manage the challenges of biomarker IP more pressing. Given the heterogeneity of approaches and experiences we have revealed it is unlikely that there is a single set of solutions to the issues raised by the trend towards biomarker IP. Policymakers who wish to support innovation in the molecular diagnostics sector whilst ensuring patient access to valuable new tests will have to adopt different strategies in different circumstances. In doing so they must accept that they are operating in uncertain and rapidly shifting terrain.

5.6 A new basis for progress in the field

The above limitations accepted, this report illustrates the strength of the case study method for hypothesis falsification. On this basis three widely-held views about gene patents can be put aside as having been negated or requiring significant qualification:

1. *Are gene patents uniquely problematic in terms of being difficult to invent around*? In fact they are not infallible, may be invented around, and other forms of IP can also be disruptive in this field.

2. *Is exclusive licensing always problematic in genetic diagnostics?* It may be, in some cases, but more could be done in the drafting of exclusive licensee agreements to include terms which might prevent some problems from emerging.

3. *Are patents on genes are sufficient incentive on their own to ensure large-scale private investment to validate tests?* They may do in some cases, but there are clearly limits to the investment firms make when faced with diverse requirements of national markets and difficulties in promoting their products across these markets; the scale of investment may be linked to the potential size of the market and likely return on investment and publicly funded research continues to play a major role in

validation of tests.