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**A molecular monopoly? HPV testing, the Pap smear and the molecularisation of  
cervical cancer screening in the USA.**

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## **Abstract**

DNA-based molecular testing for Human Papillomavirus (HPV) has emerged as a novel approach to cervical cancer screening in the context of well entrenched prior technology, the Pap smear. This paper seeks to elucidate the process of molecularisation (Clarke et al. 2003) in the context of screening programmes. We illustrate how, although Pap has long been problematized and could be seen as a competing technological option, the existing networks, and regime for Pap were important in supporting the entrenchment process for the artefacts, techniques, and new diagnostics industry entrant Digene, associated with the new test. The paper provides insights into how molecularisation of screening unfolds in a mainstream market. We reveal an incremental, accretive, rather than revolutionary process led by new commercial interests in an era when diagnostic innovation is increasingly privatised. We show Digene's reliance on patents, an international scientific network, and their position as an obligatory passage point in the clinical research field with regard to the new technology's role, as well as controversial new marketing practices. The paper is based on a mixed-method approach, drawing on a wide range of contemporary sources (including patents, statutory filings by companies, scientific literature, and news sources) as well as interviews.

## Introduction

In 2002 the US diagnostics company Digene was approaching profitability after a decade of work on a molecular alternative to the Pap smear. Their bid to enter the cervical cancer screening market had put Digene in the vanguard of companies developing new genomic diagnostics and their 2002 annual report expressed the company's ambitions thus:

We expect gene-based diagnostic tests will create a fundamental shift in both the practice of medicine and the economics of the diagnostics industry. Gene-based diagnostic tests will create an increased emphasis on preventative molecular medicine. Physicians will be able to use these tests for the early detection of disease and to treat patients on a personalized basis, allowing them to select the most effective therapy with the fewest negative side effects. Furthermore, companies that develop gene-based diagnostic tests may obtain intellectual property protection and, therefore, may generate higher margins. (Digene Annual Report 2002:2)

Digene's vision of the *clinical* potential of genomic technologies is shared by many scientists, research funders and clinicians, and the genomic turn in the life sciences has generated substantial public and private investment in research for early disease detection (exemplified by the US National Cancer Institute's Early Detection Research Network). However, Digene's *commercial* vision is not without controversy. In particular, attempts to capture the economic value of genomics through DNA patenting have met with opposition from groups of scientists, clinicians and NGOs (see Parthasarathy 2007).

Naturally, sociologists are interested in the genomic turn in biomedicine, a phenomenon whose multiple dimensions are captured in the concept of *molecularisation*. The focus on molecules in biomedical research and clinical practice can be traced back a century (de Chadarevian & Kamminga). However, many scholars follow Clarke et al in defining contemporary molecularisation in genomic terms as: "attempts to understand diseases at the (sub)molecular levels of proteins, individual genes, and genomes ... partially displacing previous emphases on germs, enzymes and biochemical compounds." (2003, p.175, see also Rose, 2007,p.12). Their view that *genomic* molecularisation is "partially displacing" earlier forms of molecularisation is central to our first research question: does the scale and pace of change suggest that the molecularisation of screening is best characterised as a process of revolution or reform? Whilst much of the hype surrounding genomics suggests the dawning of a new era, there is good reason to be wary of grand claims: the introduction of new molecular diagnostics has often been resisted and, even when adopted,

molecular techniques have often complemented, rather than supplanting alternative practices (de Chadarevian & Kamminga). This paper seeks to extend our understanding of molecularisation as a fragile and contested process by characterising its impact on mainstream screening programmes.

Our second research question relates to the commercial dimensions of molecularisation. Digene's 2002 annual report promised commercial gain as well as clinical benefit, predicting "a fundamental shift in ... the economics of the diagnostic industry" by allowing companies to achieve "higher margins" through "intellectual property protection". The latter was a reference to Digene's patents on HPV DNA, commercial assets which they used to exclude rivals from the US market. For Clarke et al, gene patents exemplify how genomic molecularisation is interlinked with the "corporatisation and commodification" of healthcare and biomedical research, (ibid,p.167, c.f. Rajan, 2006 on biocapitalism). The commodification of genomic data in the form of gene patents has particular significance for the diagnostics industry which has traditionally been a high-volume, low-margin business where companies compete on the price and technical quality of their testing platforms (Hogarth, 2007). Molecular diagnostics companies like Digene have sought to disrupt this traditional model by using DNA patents to create diagnostic monopolies and thus drive up prices. Such a shift is linked to a change in the R&D process for new tests: instead of being a process involving multiple parties, public and private, a single company plays a more central role, albeit often in collaboration with academic partners (Hogarth, 2007). Again we must be wary of overemphasising the novelty of this trend; de Chadarevian and Kamminga have described how molecularisation has always been engendered through novel configurations of links between industry, the laboratory and the clinic (p.1), but many scholars believe that in recent decades the genomic turn in the life science has intensified this process : the "corporatization of the life sciences ... has simultaneously been rapid and hegemonic on the one hand and contingent and contested on the other." (Rajan, 2006:4). Molecularisation as we conceptualise it here involves not simply the development and diffusion of new DNA diagnostics, but an innovation process quite distinct in its commercial orientation from that of the first generation of cancer screening programmes. Thus our second research question is: to what extent is the molecularisation of screening engendered through a process of corporatisation linked to new business models in the *in vitro* diagnostics (IVD) industry?

Our choice of case study allows us to build on Casper and Clarke's seminal account of how the Pap test has been "massaged and manipulated" to transform it into a reasonably "'right' tool" for cervical cancer screening (1998). Their paper was an explanation of what we might term the Pap paradox: the test is widely credited with lowering cervical cancer mortality internationally, and has

been described as “the most effective screening test for cancer that has ever been devised.” (Dehn 2007), however, with 15%-50% false-negative rates (i.e. failure to identify cervical cancer when it is present), the pap has long been problematised as expensive, subjective and error prone (Cox and Cuzick 2006). The test requires highly-trained laboratory personnel (cytologists) who examine cervical epithelial cells by microscope, and, whilst cytology retains its primacy in cervical cancer screening programmes, there have been protracted and expensive attempts to replace or automate the Pap technique (Casper and Clark 1998, Keating and Cambrosio 2003). Digene’s DNA-based Hybrid Capture test does not detect cervical cancer but instead identifies specific Human Papillomavirus (HPV) infections associated with the onset of cervical cancer. This paper describes this most sustained challenge to the Pap’s long primacy and explores the dynamics of molecularisation in the context of one of the most established prior technologies in screening.

Like Casper and Clarke we do not offer a symmetrical account giving equal weight to all actors, but focus on the company which has dominated HPV testing in the USA, to provide an account of the market forces which play an increasingly central role in screening innovation. Medical screening in the United States is delivered within a complex health care system in which the private sector plays the primary role. Delivery of publicly-funded healthcare is increasingly in the hands of for-profit hospitals and 70% of healthcare insurance is privately provided by health insurers, health maintenance organisations (HMO) or preferred provider organisations. This complex institutional architecture shapes screening services in a number of ways, for instance the search for cost-efficiencies has encouraged the growth of handful of major commercial reference laboratories who collectively deliver a significant portion of clinical testing in the USA, making pathology big business. Cancer screening programmes such as the Pap smear are lucrative commercial markets as they involve large populations subject to regular repeat testing, and have facilitated the emergence of novel service configurations such as the breast care centres which provide mammography and subsequent treatment for women who test positive. It is this highly commercialised testing market which Digene sought to exploit with its new molecular technology.

Building on the prior insights of Clarke and colleagues, this paper uses an established STS framework developed by Blume (1992) as a lens to make a contribution to the sociology of screening by exploring and extending the concept of molecularisation, and delineating how this process unfolds in the context of major screening programs for HPV in the USA.

## Method

Developing a robust history of the first FDA-approved test for the detection of HPV required a mixed method historical process study (Van de Ven 2007). First we undertook exploratory searches of trade and scientific literature and diagnostics industry news websites. Additionally patent literature searches<sup>1</sup> and bibliographic searches revealed key investors and organisations in the HPV field. Using these data 12 interviewees were selected based on their involvement with developments in HPV diagnostics in the USA and EU. We were further informed by numerous additional interviews undertaken to understand the nature of the diagnostics sector as a whole.<sup>2</sup> Semi-structured interviews of 40-150 minutes were recorded and fully transcribed. Interviews have well-documented limitations as sources for recent histories (Hughes 1997). In particular social scientists need to be reflexive about interviewees' partisan nature, and should triangulate data from different sources (Van de Ven 2007). We therefore used interviews selectively, primarily to identify key themes and events. Triangulation involved using a range of contemporary sources to reach convergent findings. Technical accounts from scientific literature, statutory filings by companies, patent documents, and commercial databases on corporate biotech activities are particularly advantageous as unlike anonymous interviewees, these are subject to peer reviewers, patent examiners or statutory requirements on corporate disclosures. Less rigorous sources such as mainstream and biomedical news articles can still reveal view points and aid chronology. Additionally we used available scholarly histories (Reynolds and Tansey 2009, Casper and Clark 1998).

## Conceptual approach

Our conceptual framework for charting molecularisation characterises 'technology' as a 'sociotechnical ensemble' (Bijker, 1995) of artefacts, and techniques embodied in people, and whose operations are structured by a regime of norms, regulations and organizational constraints. This builds on prior categorisations of co-evolving technology components (e.g. Fleck, 2000) and looks beyond artefacts such as devices or therapeutics that were the focus of much prior work on medical innovation (e.g. Gelijns and Rosenberg, 1994; Blume 1992 Martin, 1999). Embracing alternative approaches such as Keating and Cambrosio's (2003) 'biomedical platforms' and Parthasarathy's (2007)

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<sup>1</sup> The study required a full 'patent landscape' to be generated to reveal commercially active organisations - See Hunt et al 2007 for description of patent search methods.

<sup>2</sup> This work was undertaken as part of an international comparative study of the impact of patenting on diagnostics, sponsored by the European Commission's JRC-IPTS. The study drew on more than 70 interviews in the EU and USA covering aspects of patenting in relation to diagnostic innovation, and focusing on specific case studies.

'medical architectures' we stress the importance of wider institutional and structural influences on technology.

Following previous work (Hopkins 2004, 2006), we adopt Blume's framework (1992) to capture such influences. Here, technological innovation is conceived as occurring through the formation of networks of actors who shape these artefacts, techniques and regimes, according to a shared vision of its future application. As in the social worlds perspective we reject the notion that non-human actors have as much influence as human actors (Casper and Clark 1998).

In order to highlight key features of the evolution of HPV testing and screening we utilise four key concepts drawn from Blume's work: *problematization*, *inter-organisational links*, *visions*, and the *career*. Blume suggests that technology evolves through a series of *problematizations*, whereby groups of actors seek to address features of their environment, a technology or its usage that they find problematic. Influential actor groups often occupy a position of power over others in the network and such influence is traceable through *inter-organisational links* (e.g. contracts to provide services, grant provision, formal or informal research collaborations). Influence may also be found in explicit statements of intent to the future shaping and application of technology. These *visions* (exemplified by the statement from Digene's 2002 annual report above), are an important way of enrolling support by appealing to common objectives. These dynamics of technological innovation can be followed longitudinally using Blume's concept of the *career*, a sequence of milestones and phases (exploration, development, adoption, and growth) which mark the trajectory from bench to widespread practice.

Blume's framework can accommodate insights from a range of related studies and concepts in biomedicine. The central focus on networks and inter-organisational links provides opportunity to observe processes of entrenchment of new and old technologies in which actors, linkages, and visions of technological options become mutually attuned - see Koch and Stermerding's (1994) study of molecularised Danish cystic fibrosis screening. This helps to reveal actors' difficulties in constructing or re-configuring networks and regimes to accommodate or make acceptable new technological options (ibid). In this paper we identify the importance of particular problematisations, organizational links and Digene's vision within each of the four phases of the career of the HPV screening test and use Blume's framework to frame the analytical concepts described above.

## The four phases of the HPV test's career

### 1.Exploration (1983-1988)

In 1983 Professor Harald zur Hausen's team at the German Cancer Research Centre discovered an association between HPV type 16 infections and cervical cancers. Their viral infection-mediated model of cervical cancer (later awarded a Nobel prize) was initially highly controversial. Overcoming this resistance required the opening of new fields of research, in part led by companies seeking to develop new technological options for cancer vaccines and diagnostics (Reynolds and Tansey 2009), including new competition for the Pap test.

During the mid-1980s researchers at laboratory-supplier BRL-Life Technologies (BLT) began work on a commercial HPV test. Local collaborators (researchers, clinicians and pathologists) at Georgetown University provided them with graded cervical cancer samples. Initially BLT's goal was to understand the epidemiology of HPV types 16 and 18 in patients, essential data for clinical validation of an HPV test. However, they discovered that many of their samples were not infected with these known high-risk HPV types. Thus the researchers, led by Attila Lorincz, turned to identifying novel HPV types discovering and cloning a number of high-risk strains, their collaborators at Georgetown making other important discoveries (see Table 1). This work placed Lorincz at the forefront of international research on HPV and cervical cancer, alongside George Roth at the Institut Pasteur in France. Like his French counterparts Lorincz patented his discoveries, something which zur Hausen had not done and a move which would prove as important to Digene's future success as Lorincz's growing scientific reputation.

Even at this stage we can see how the commercial development of the HPV test required the creation of inter-organisational links (Blume 1992) with academics and clinicians enmeshed in the established regime of cytology screening. BLT's research identifying new HPV types illustrates how the corporatisation of biomedical research undermines any simple model of basic research as an academic function, and the patenting of HPV strains by both BLT and their academic counterparts illustrates how the commercialisation of biomedical research has become entrenched in the practices and values of public institutions.

**Table 1: Features of three generations of HPV test – Applications, HPV types , IP, and artefactual embodiment**

Test Name (Owner) FDA approval year	HPV types included in test (patented HPV types underlined)	Artefactual embodiment of technique
Virapap (Life Technologies) FDA approved 1988	16 18 31 <u>33</u> <u>35</u>	Radioactive Kit for manual technique (Southern Blot test)
Hybrid Capture Tube Test (DiGene)  FDA approved for ASCUS trriage in 1995	16 18 31 <u>33</u> <u>35</u> <u>39</u> 45 51 <u>52</u> <u>56</u>	Kit for antibody + DNA/ RNA hybrid based w/ instrument for machine read (luminometer, screen, and print out)
Hybrid Capture 2 (DiGene)  FDA approved in 1999 for ASCUS triage and 2003 for screening.	16 18 31 <u>33</u> <u>35</u> <u>39</u> 45 51 <u>52</u> <u>56</u> 58 59 <u>68</u>	Kit for antibody + DNA/ RNA hybrid based w/ automated instrumentation platform with windows-based software for readouts and data storage.

**2.Development (1988-1999)**

In 1988 BLT became the first company to gain FDA approval for an HPV test: the ‘Virapap’ kit composed primarily of synthetic nucleic acid probes. However, despite some clinical uptake, regulatory approval did not prevent commercial failure due to *problematizations* (Blume 1992) of its technology: Virapap was radioactive so had a short shelf life, was potentially hazardous to lab staff, and it was not able to detect a sufficient range of HPV types (of which many were increasingly being discovered). Furthermore many pathologists and cytologists had expressed profound scepticism about the utility of HPV testing, perhaps unsurprising given that the status of HPV as the cause of cervical cancer remained contested at this time (Reynolds and Tansey 2009).

In 1990 a frustrated BLT sold their molecular diagnostics division to Digene, a small rival with its own HPV technology. Virapap’s failure informed Digene’s future strategy. While others continued to identify dozens of new HPV types, Digene developed a new detection technique, which they named Hybrid Capture (HC). Patented in 1992, this was a non-radioactive method (see Table 1) for detecting specific HPV strains by hybridising HPV DNA from clinical samples with complementary RNA sequences in the kit. Detection of HPV was through antibodies that ‘captured’ the DNA-RNA hybrids created from an HPV infected sample. Its key technical advantage was improved sensitivity

to HPV strains. Digene’s HC test outperformed rivals reliant on widespread techniques that were too sensitive, even showing positive results to air-exposed swabs that had picked up background particles of the ubiquitous virus (Lorincz et al. 1992, Reynolds and Tansey 2009).

Digene hoped their new HC kit would become, in Casper and Clark’s terminology (1998), the “right tool” for HPV testing. However, clinical adoption of this proprietary technology needed consensus on what job it should be doing in cervical cancer screening programmes.

We thought that a molecular determination of the virus that causes cervical cancer could minimally provide additional new information to the cytologists and the pathologists to help them improve the quality of the Pap smear, but we had it in the back of our mind that maybe the Pap smear was not as great as it had been claimed, and that ... we might be able to find a superior method, either a more sensitive or more specific or more prognostic in some way. So yes, that was, that was in our minds all right: that the Pap smear was competition. (Digene Executive)

This illustrates firstly how Digene’s *clinical* vision for the molecularisation of cancer screening centred on a problematisation of the Pap test and the promotion of HPV testing as a solution to the limitations of the entrenched technology, but secondly their uncertainty about whether molecularisation would entail supplanting or merely supplementing the Pap test. Table 2 illustrates the range of options, ranging from a subservient role to a dominant one for the HPV test.

Addressing this uncertainty in hope of overcoming clinical resistance to HPV testing, was the second element in Digene’s strategy to avoid Virapap’s fate. Pursuit of this strategy required Digene to broaden their network and make significant financial investment in clinical trials.

**Table 2 Three possible roles for HPV testing in cervical cancer screening**

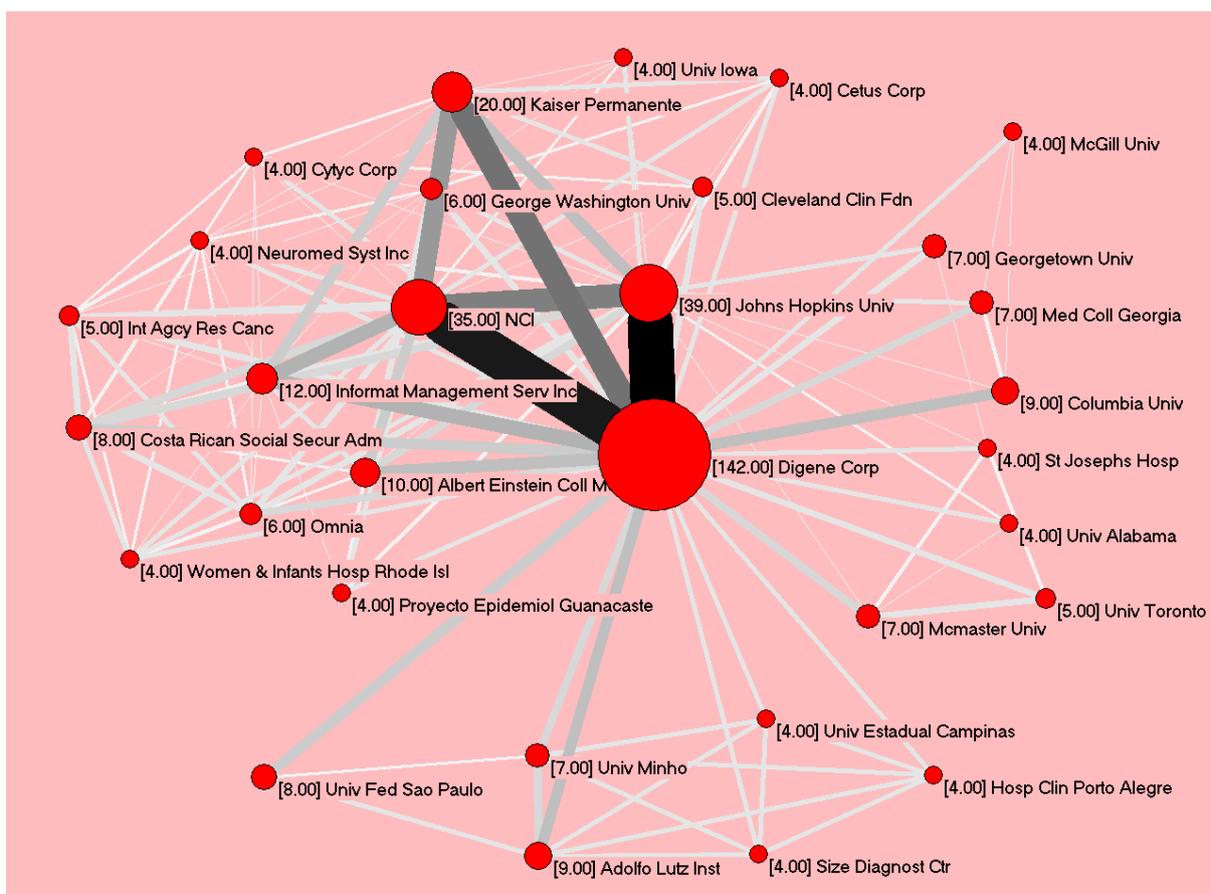
Testing protocol	Description	Molecular status
ASC-US triage (reflex)	Pap remains initial screening test, HPV is used as a reflex follow-up for ambiguous results, reducing need for colposcopy.	Subservient
Adjunctive screen with pap	Pap and HPV used as joint primary screen, allowing less frequent screening for women who test negative for both tests.	Equal
Sole primary screening test	HPV used as initial screening test, pap is used to follow-up HPV-positive women.	Dominant

During the 1990s Digene invested in multiple large head-to-head clinical studies against the Pap test, in a series of collaborations with charities, government departments, universities and research institutes across the world. By 2003, Digene had participated in HPV tests involving “an aggregate of approximately 90,000 women on four continents” (Digene 2002:12) and increased their annual R&D

expenditure to \$10,262,000. This made Digene the primary sponsor and shaper of HPV clinical trials, placing them at the centre of a global research network, illustrated by Figure 1 which shows links with key scientific collaborators (i.e. four or more co-authored papers). The strong inter-organisational links with NCI, Johns Hopkins and the Managed Health Organisation, Kaiser Permanente, are particularly clear.

Digene collaborated with Kaiser Permanente and NCI on two studies crucial to adoption of the HC2 test for use in ASC-US triage (see Table 2). Digene gained FDA approval for use of the HC2 test in ASC-US triage in 1999. This suggests that, at this stage in the career of their technology, Digene was taking a cautious approach to molecularisation of cervical cancer screening in the US market, seeking to support rather than supplant the *entrenched* (Koch and Stemerding 1994) gold standard, the Pap test. FDA approval marks the end of Blume’s *development phase*.

**Figure 1: Map of Digene Corporation’s main co-authorship links on scientific papers**



Source: ISI publications data for ‘Digene’, displayed using the Kamada-Kawai algorithm in Pajek freeware (with no weighting for line similarity, node size relates to number of co-authored papers).

### **3. Adoption 1999-2003**

This period saw Digene's HC2 test become entrenched in cervical screening in the USA: by 2003 Digene had gained key customers, such as the major reference laboratories, giving them 62% of the AS-CUS triage market and the company had finally become profitable. Pivotal to adoption was data from the NCI-funded ALTS trial (for which Digene provided supplies free of charge). Data from this trial was crucial for the inclusion of HPV testing in clinical guidelines by the American Society for Colposcopy and Cervical Pathology (ASCCP): "It [the ALTS trial] validated the performance of the test in predicting CIN 3. It was such a widespread study and the recommendations based on that through ASCCP pretty much directed the growth of that test." (US LAB 2). The guidelines state that clinical data from multiple studies had proved (providing a suitable sample was collected with the initial pap test) that HPV testing was a better way of triaging women with AS-CUS than traditional options of repeat cytology or immediate colposcopy. The justification for the recommendation highlights how the test was valued for the ease with which it could be added to the existing cytology-based screening process: "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." (Wright et al, 2002) Further support came in 2002 in guidelines issued by the American Cancer Society (ACS).

Digene had a growing clinical evidence base, externally validated through peer review, FDA approval and endorsement in clinical guidelines. To speed adoption of their test, Digene made large investments in sales and marketing. The traditional marketing route for diagnostic companies is to enrol the support of laboratory directors who then promote new tests to physicians. However, Digene employed a dedicated sales force directly targeting physicians, a strategy seen by some investors as essential to drive rapid adoption of new molecular diagnostics [personal communication with US venture capitalist], and observed in other genetic test developers, such as Athena and Myriad Genetics (SACGHS, 2010).

The extent of Digene's network is illustrated by the ASCCP and ACS guidelines. Amongst the 41 members of the ASCCP working groups who contributed to the guidelines, there were seven individuals disclosing links with Digene, ranging from study grants to honoraria and consultancy work. Similarly five of the 38 working group members for the ACS guidelines disclosed some link to Digene. Both guidelines stated that only studies using the HC2 test had been taken into account when assessing the utility of HPV testing, indicating the extent to which Digene's R&D investment had given it a dominant position in the HPV-testing research network.

#### **4.Growth (2003-present)**

Following adoption of the test for triage, Digene focused on the larger primary screening market (see Table 2), while growing sales and the market entry of other companies signalled widespread validation of the molecular approach to cervical cancer screening.

Use of Digene's test for triage of AS-CUS cases was the low-hanging fruit of HPV testing. It exploited a chief clinical problematisation of Pap testing, namely the large number of ambiguous results requiring further follow-up, but did not challenge Pap's status as the gold standard. It was, moreover, a relatively small market. Perhaps unsurprisingly, most of Digene's R&D investment was focused on the more lucrative primary screening market, funding studies where HPV testing was a routine adjunctive screen alongside the Pap test or an alternative to it. In 2002 guidelines from the American Cancer Society (ACS) recommended HPV testing as an adjunctive screen in women over 30 (again citing only studies funded by Digene) and in 2003 this indication gained FDA approval. The advantage claimed for the combined screening technologies was that women with negative results need not to be tested again for three years (in the USA annual Pap testing was the standard of care). The HC2 was renamed DNAwithPap, an indication of Digene's vision of a future where the molecular and the cytological were inextricably linked. Long-time Digene collaborators Kaiser Permanente were early adopters, again demonstrating the importance of key inter-organisational links, but also illustrating the significance of institutional structures in building early adoption:

The Kaiser Permanente HMO model was ideally suited in some ways to making such a drastic change. First, because Kaiser directly cares for its paying members, it did not have to convince outside payors to cover the additional test. Second Kaiser employs its physicians, so if the administration wanted to add a new laboratory test, it could do so without formal buy-in, though implementing the test requires the understanding and cooperation of the ob/gyn providers" (Southwick,2004)

Elsewhere clinician-adoption was slow for this screening protocol. Compliance with the new guidance required physicians to forgo annual examinations with patients who tested negative with Pap and HPV tests (Southwick 2003), thus challenging what one pathologist described as "the strongly ingrained emphasis on annual Pap smear screening" (Stoler, 2001). Digene responded by adopting a new marketing strategy: direct-to-consumer (DTC) advertising. When Digene's ad campaign launched, the media reported public and professional disquiet. Amongst those quoted in

the media was Dr Alan Waxman, co-author of the ACOG 2003 guidelines, and a sceptic about adjunctive HPV screening: "It's another way of screening ... But to recommend it would give it higher priority over the Pap alone, and I don't think the data is there to support that." [Rosenwald, 2005]

### **A molecular monopoly - protecting market share**

Despite such clinical resistance the HPV market has grown rapidly. Most insurance companies cover HPV testing; it is mandated by a number of states such as California and Maryland, and available through the public Medicaid system in most states. Industry estimates suggest more than 10 million tests are performed annually and that the market has grown 40% in each of the past five years. However, not all HPV testing is done using Digene products. A 2006 survey suggested that other tests were being used in 19.1% of US labs, either alongside Digene's HC2 test, or instead of it (Moriarty, 2008). Testing labs were developing their own tests from scratch or using component reagents sold by companies such as Ventana and Third Wave. Digene sought to restrict such competition by using its intellectual property rights and the FDA regulatory regime as barriers to market entry.

Digene had a legal monopoly through the right to exclude others from commercialising tests on the high-risk HPV strains they had patented or licensed for diagnostic use in the USA (see Table 2). Between 2001 and 2009 Digene defended their dominant patent position in a series of US law suits with rivals Gen-Probe, Roche, Beckman Coulter and Third Wave. Digene further reinforced their proprietary defences through a strategy of technological autarky. Many molecular diagnostics companies focus on producing reagents which can be run on other companies' platforms but Digene chose to create its own self-contained instrumentation system to ensure they were not dependent on potential rivals: "...we didn't want to be subject to the vagaries of the other company who was at any moment going to be our competitor ..." (Digene Exec.).

Digene exploited their status as the only company with an FDA-approved test clinically validated in multiple large studies as a further way to try and protect its market hegemony: "Digene set the bar very high and FDA have kept it high." (US industry executive). This argument was set out in the ACSSP's 2001 guidelines: "[The] bar has been raised for bringing forward newer HPV diagnostics ... Any new test must document its performance relative to this standard". In 2006 new ACSSP guidelines went further, suggesting less validated tests "may increase the potential for patient harm". These statements illustrate how Digene's test had become the gold standard (Bowker and Star 1999) for HPV testing.

Controversy about the use of tests which have not been approved by FDA, was raised in 2005 in an article in *CAP Today*, the magazine of the College of American Pathologists. The article quoted Digene's NCI collaborator, Marc Schiffman: "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 was 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."

Digene's dual strategy was largely successful in excluding rivals in the US market but it was ultimately unable to prevent Third Wave from launching an FDA-approved test, ending Digene's near decade as monopolist. However, by this time Digene had been bought for \$1.6Bn by the Dutch company Qiagen, a price which demonstrated the commercial success of Digene's strategy and the perceived value of the HPV test, as Digene had little else in its development pipeline (Baker 2006).

Yet, for HPV-testing sceptics the scale of this acquisition simply confirmed that cervical cancer screening was under threat from the forces of commercialism. In a lengthy 2008 editorial defending the role of cytology, the pathologist R Marshall Austin sounded the alarm: "No one observing the changing field of cervical cancer screening could now reasonably overlook the multi-billion dollar financial interest just behind the scenes, nor industry's close affiliations with scientific thought leaders and organizations." (p156) The article presented cytotechnologists as the guardians of quality cervical cancer screening and urged the continuation of education programmes for cytologists.

Despite such clinical resistance, commercial interest continues to be fuelled by Digene's vision of a molecular HPV test to replace cytology: "All the players in the market are betting on the transition to a model where all women get the [HPV] test first. This would increase the size of the market by tenfold." (US industry executive). The enduring power of Digene's vision continues to be sustained by their R&D investment and the network of collaborations it spawned, such as the UK-based HART trial whose findings were published in *The Lancet* where Cuzick argued that Digene's test could be used as the sole primary screen, with Pap testing relegated to a secondary role as a follow-up test for HPV-positive women (Cuzick, 2003). By 2006 at least some US pathologists were suggesting that the end of Pap testing was in sight: "New studies and current data suggest that with increasing sensitivities, we may see women moving from the HPV test in combination with Pap to the HPV screen alone." (Borgert, 2006) For now such predictions remain visionary

statements which indicate that the molecularisation of cervical cancer screening is a process which has yet to run its course.

## 5. Discussion

Given the huge levels of public and private investment in genomic research, increasing number of molecular screening technologies are likely to enter clinical practice in coming decades. It is therefore important to gain a clearer understanding of the social dynamics of innovation in this field. We have sought to answer two key questions: does the scale and pace of change suggest that the molecularisation of screening is best characterised as a process of revolution or reform, and to what extent is the molecularisation of screening engendered through a process of corporatisation linked to new business models in the *in vitro* diagnostics (IVD) industry? Our history of HPV testing has used Blume's established conceptual framework for tracking the co-evolution of the networks, artefacts, techniques and regimes. This conceptual lens has allowed us to extend the utility of the sociological concept of molecularisation in the context of cancer screening.

HPV testing has been available for nearly 20 years, and is the most commonly used molecular technology for cancer screening, but it has failed to supplant Pap; instead the molecularisation of cervical cancer screening has required an accommodation with cytology. This reflects the wider picture in oncology, where diagnosis still relies on morphological examination of tumour biopsies. This evolutionary model would appear to be consistent with the broader history of diagnostic innovation in the twentieth century: "The newer modes of analysis have not necessarily replaced the older ones. In many ways, the history of these techniques has been one of continuous accretion ..." (Amsterdamska and Hiddinga p.426). This mirrors the uptake of biotechnology in pharmaceutical R&D processes, where new biotechnological techniques were used to re-invigorate traditional small molecule drug discovery as well as supporting the development of novel biologic therapies (Hopkins et al. 2007).

Our account of the Pap's persistence as the gold standard for cervical cancer screening supports Bowker and Star's (1999) contention that established standards have significant momentum and may endure over long periods of time because they span multiple communities of practice (in this case cervical cytologists and obstetrician/gynaecologists). However when problematised, they may be opened up, but the new practice must also submit to the growing need in the era of evidence-based medicine for multiple forms of standards (Timmermans and Berg 2003). This would appear to be a key site of contestation in the molecularisation of screening, both caught up in a technological accumulation to support the wider thrust for higher standards of care. Molecular diagnostics

companies like Digene present their products as inherently more standardised and standardisable than older techniques, but their success in challenging established standards will be contingent on multiple factors.

How then should we characterise the process of molecularisation? Clarke et al suggest that technoscientific innovations in biomedicine are cumulative and do not immediately replace older alternatives, but that nevertheless they “tend to drive out the old over time” (p184). However, the HPV/Pap story suggests that the molecularisation of screening may not be a zero-sum game in which the new eventually triumphs at the expense of the old; instead, novel genomic technologies may simply further entrench older rivals. It seems the addition of HPV to established testing protocols is simply the latest chapter in the story set out by Casper and Clarke (1998) of how successive forms of tinkering were necessary to ensure that Pap testing remains the “right tool for the job”

Our second research question concerned the relationship between molecularisation and commodification and corporatisation. The history of laboratory diagnostics in the twentieth century was one of professionalization and the creation of new sub-disciplines such as microbiology and radiology. The Pap smear exemplified that trend, predicated as it was on the creation of a new cadre of cytology specialists (Casper and Clarke 1998). The promotion of Pap testing was largely carried out by non-profit organisations such as the American Cancer Society (ibid.). By contrast, HPV testing exemplifies a new trend: the increasing importance of diagnostic companies in the development and diffusion of innovative molecular diagnostics.

Digene’s enrolment strategies involved a dynamic process of deepening engagement. In the first place it suited clinical researchers to collaborate with Digene, who might either subsidise or pay for clinical trials. Secondly, as early data demonstrated the robustness of their test, it gained credibility as a dependable research tool whose use in multiple trials across the globe could be expected to produce reliable standardised data which could be subject to cross-comparison and meta-analysis. Finally, as the research community began to produce findings which indicated a possible role for HPV testing in cervical cancer screening, these researchers became advocates for the clinical use of the HC2 technology, as the only HPV test which had proven its value in multiple large clinical trials. Digene thus exploited a growing interest in the clinical potential of HPV testing which they harnessed to create an international research network focused on demonstrating the clinical utility of their proprietary HC technology. Digene’s problematisation of the research agenda conflated the utility of HPV testing and the utility of their HC test and this allowed them to become an obligatory passage point (Callon, 1986) for clinical research on HPV testing.

The success of Digene's problematisation required not only a critique of the Pap test but the establishment of their proprietary technology as the tool of choice for detecting the presence of HPV. This was not simply a question of which company had the most reliable, accurate or convenient technology but also a matter of intellectual property rights, closely related to Digene's *commercial* vision of higher profit margins from patent-protected diagnostics. Digene's success was achieved by not only by enrolling key supporters to drive clinical adoption; but also by excluding competitors from joining the network.

Their strategy's success relied in large part on Digene's scientific reputation for research on HPV and cervical cancer. However, the company's substantial investment in clinical trials was equally important. This case illustrates how a young, relatively small diagnostic company can become the orchestrator of global networks involving research scientists, funding agencies, laboratory directors, clinicians, patients and regulatory agencies. This is a new role for diagnostics companies, illustrating how molecularisation involves not simply a greater role for industry but a shift in business models. Crucial aspects of Digene's commercial strategy - patenting biomarkers such as HPV's DNA to try and gain a period of market exclusivity: marketing direct to physicians, direct to consumer advertising, investing heavily in studies to demonstrate the clinical utility of a test – were all relatively novel to the IVD industry. For critics the strength of Digene's network and its direct-to-consumer marketing strategy were sources of concern. For their supporters, they demonstrated that the company were trying to do the right thing: investing heavily in clinical trials to explore the utility of HPV testing, and helping to raise awareness of the benefits of a validated technology which could help save women's lives. Again we see how collaboration was facilitated by a shared vision which aligned Digene's private interests and the wider public interest.

However, the novelty of the commercial drivers should not deflect attention from the continuities with the Pap story. Public bodies played a pivotal role in the promotion of Pap testing (Casper and Clarke 1998) and were also central to the clinical adoption of the HPV test, especially the NCI who funded the ALTS trial and (alongside the ACS) then championed Digene's HC2 technology as the only robustly-validated HPV test. The entrenchment of the HC2 test in screening protocols required Digene to enmesh itself in this pre-existing network of actors, just as it required a technical accommodation with the entrenched Pap smear.

The molecularisation of cervical cancer screening remains highly contested by sceptics doubtful of its clinical utility and wary of its commercial orientation. As Austin's 2008 editorial indicates, their critique is also a defence of the traditional authority of the medical profession as the arbiters of clinical truth and the guardians of patient care. Austin formulated an alternative problematisation to

frame the Pap-HPV debate, suggesting that more was at stake than competing claims for the diagnostic accuracy of rival technologies, instead arguing that ““much of the (US) physician-patient relationship is built on the regular Pap visit.”” (p156) The Pap is not just a test; it is an annual clinical encounter. By presenting the HPV test as a fundamental threat to the stability of the relationship between doctor and patient, Austin indicates not only how contested the molecularisation of cervical cancer screening is, but also how contingent it may be on accommodation with the established medical order and the entrenched technologies which currently underpin it.

## **Bibliography**

ACOG (2003) Cervical cytology screening, ACOG Practice Bulletin, 45, August

ACOG (2009) Cervical cytology screening, ACOG Practice Bulletin, 109, December

Amsterdamska O and Hiddinga A (2003) ‘The analyzed body’ in Cooter, R and Pickstone, J (eds) *Companion to Medicine in the Twentieth Century*. London: Routledge

Bijker, W. E. (1995) *Of Bicycles, Bakelites and Bulbs: towards a theory of sociotechnical change* Cambridge, MA: MIT Press

Baker, M. (2006) ‘New-Wave Diagnostics’ *Nature Biotechnology* 24(8) pp. 931-938

Blume S. (1992) *Insight and Industry: on the dynamics of technological change in medicine*. Cambridge, MA:MIT Press

Borgert, N. (2006) ‘Testing providers work to improve cervical cancer diagnostics’, *Clinical Lab Products*, accessed online at [http://www.clpmag.com/issues/articles/2006-10\\_07.asp](http://www.clpmag.com/issues/articles/2006-10_07.asp)

Bowker, G and Star S (1999) *Sorting things out: classification and its consequences*. Cambridge:MIT press.

Callon, M. (1986) ‘Elements of a sociology of translation: domestication of the scallops and the fishermen of St Brieuc Bay.’ In Law, J. (ed) *Power, Action and Belief: A New Sociology of Knowledge?* London, Routledge.pp. 196-233.

Casper, M. and Clarke, E. (1998) ‘Making the Pap Smear into the ‘Right Tool’ for the job: cervical cancer screening in the USA, circa 1940-1995.’ *Social Studies of Science*, Vol. 28, pp.255-290.

Cox, T. and Cuzick,J. (2006) HPV DNA testing in cervical cancer screening: from evidence to policies, *Gynaecologic Oncology* Vol. 103, pp.8-11.

Cuzick,J et al (2003) Management of women who test positive for high-risk types of human

papillomavirus: the HART study. *The Lancet* 2003; 362: 1871–76.

de Chadarevian, S. and Kamminga, H.(eds) *Molecularizing Biology and Medicine: New Practices and Alliances, 1910s-1970s*. Amsterdam:Harwood, 1998

Dehn, D. et al (2007) 'Human papillomavirus testing and molecular markers of cervical dysplasia and carcinoma.' *Cancer* Vol. 111( 1) pp. 1-14.

Digene (2002) Annual Report, available online at <http://secwatch.com/dige/10k/annual-report/2002/9/30/4393963>

Fleck, J. (2000). "Artefact-activity: the co-evolution of artefacts, knowledge and organisation in technological innovation." In J. Ziman (Ed) *Technology as an Evolutionary Process*. Oxford, Oxford University Press: 248-266.

Gelijns, A. and Rosenberg (1994). 'The dynamics of technological change in medicine.' *Health Affairs* (Summer): 28-46.

Hogarth, S. (2007) *The clinical application of molecular diagnostic technologies – a review of the regulatory and policy issues*. Report for Health Canada, Cambridge: University of Cambridge.

Hopkins, M. (2004) *Technique-led technological change and the hidden research system: genetic testing services in the NHS*, DPhil Thesis, SPRU, University of Sussex.

Hopkins, M., P. Martin, P. Nightingale, A. Kraft, and S. Mahdi (2007): *The Myth of the Biotech revolution: An assessment of technological, clinical and organisational change*. *Research Policy*, 36(4), 566-589.

Hopkins, M. (2006) *The hidden research system: the evolution of cytogenetic testing in the National Health Service*. *Science as Culture*. 15 (3): 253-276.

Hughes, J. (1997). "Whigs, prigs, and politics: problems in the historiography of contemporary science." In Soderqvist (Ed) *The Historiography of Science and Technology*. Amsterdam, Harwood Academic Publishers: 19-37.

Keating P and Cambrosio A. (2003) *Biomedical platforms: Realigning the Normal and the Pathological in Late-Twentieth-Century Medicine*. Cambridge Mass.: MIT Press

Koch, L. and Stemerding, D. (1994) *The sociology of entrenchment: a cystic fibrosis test for everyone*, *Social Science and Medicine*, 39, 9, 1211–20.

Levenson, D. (2007) *New HPV test brings challenges*, *Clinical Laboratory News*, 33,6, 1

Lorincz A.T., R. Reid, A. Bennett Jenson, M.D. Greenberg, W. Lancaster, R.J. Kurman (1992) 'Human Papillomavirus Infection of the cervix: Relative Risk Associations of 15 common Anogenital types' *Obstetrics and Gynecology* Vol. 79 (3) pp. 328-337.

Moriarty A. et al. (2008) *Human papillomavirus testing and reporting rates: practices of participants in CAP's Interlaboratory Comparison Program in Gynecologic Cytology in 2006*, *Arch Pathol Lab Med.*, 132, 1290–1294

Parthasarathy, S. (2007) *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care*. Cambridge, MA: MIT Press.

Martin, P.A. (1999) 'Genes as drugs: the social shaping of genetherapy and the reconstruction of genetic disease' *Sociology of health and Illness*. Vol. 21 No.5 pp. 517–538

Reynolds, L A and E M Tansey (eds) 2009 'History of Cervical cancer and the role of the Human Papillomavirus, 1960-2000' Wellcome Trust Witness Seminar Series Volume 38.

Rosenwald, M (2005) 'Digene's Ads Take Their Case To Women' *Washington Post* Monday, March 21.

Southwick (2004) Kaiser roll: the push for more HPV screening, *CAP Today*, July.

Stoler, M. (2001) HPV for cervical cancer screening: is the era of the molecular Pap smear upon us? *Journal of Histochemistry & Cytochemistry*, 49,9, 1197–1198

Timmermans, S. and Berg, M. (2003) *The Gold Standard*. Philadelphia: Temple University Press

Van de Ven, A. H. (2007) *Engaged Scholarship*. Oxford University Press.

Titus, K. (2005) Making a valid point about HPV tests, *CAP Today*, September, 76–82.

Wright, T. et al. (2002) 2001 'Consensus guidelines for the management of women with cervical cytological abnormalities.' *JAMA*, 287, 16, 2120-2129.

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.