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Chapter 5

Technological accretion in diagnostics HPV testing and cytology in cervical cancer screening

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5 Technological accretion in diagnostics

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Introduction

This chapter follows the emergence of molecular HPV testing technologies and their application to cervical cancer screening in the USA. When HPV testing was first commercialised in the late 1980s, screening for cervical cancer had been a routine part of preventive healthcare for at least two decades, with testing conducted by cervical cytologists using the Pap smear test, a technology first developed in the 1910s. Many now predict that molecular HPV tests will eventually replace cervical cytology, bringing fundamental changes to the clinical infrastructure of screening in the process. However, at present these technologies not only co-exist but augment each other. This process of technological accretion has involved not only an accommodation with molecular technologies, but also the widespread adoption of novel cytology technologies: liquid-based cytology (LBC) and automated slide readers. This chapter explores the institutional factors that have shaped this contingent outcome. We begin by setting out the clinical context of cervical cancer screening.

Cervical carcinoma is the fourth most common form of cancer in women, and is the cause of 7.5 per cent of cancer deaths in women worldwide (IARC 2012). These global statistics belie a grossly unequal disease burden: cervical cancer is now predominantly a disease of low- and middle-income countries because, since the 1960s, both incidence and mortality rates have dropped dramatically in many developed countries. This is generally ascribed in large part to the introduction of screening programmes. Cervical cancer screening (CCS) has become ubiquitous in the developed world with many countries running national programmes to ensure that women have the opportunity for regular screening. Statistics from the USA show a greater than 50 per cent decline over 30 years in both incidence and mortality, which are widely attributed to cervical cancer screening, although the disease still kills around 2.38 in 100,000 women in the USA (ACOG 2012). The decline in incidence and mortality is due primarily to that fact that screening identifies pre-invasive lesions that can be treated well before the possible onset of cancer (Saslow *et al*. 2012).

Until recently cytology-based screening has relied on a technology developed in the first half of the twentieth century: the Pap smear. The traditional Pap smear involves scraping cells from the cervix and smearing them in a thin layer on a glass slide. The cells are then stained and examined under a microscope by a cytologist to check for abnormalities. In the 1990s the traditional Pap began to be replaced by liquid-based cytology – a technique that involves placing the cells into preserving fluid and then filtering them to remove impurities prior to examination by microscope. However, even before LBC became routine, a more radical alternative technology was in development. In 1983 scientists provided strong evidence for an association between cervical cancer and human papilloma virus (HPV) when they cloned two carcinogenic HPV types (HPV 16 and 18) and, soon thereafter, companies began to develop HPV tests for use in cervical cancer screening.

Method

Developing a robust history of HPV testing in the USA required a mixed method historical process study that triangulates several data sources (Van de Ven 2007). First we undertook exploratory searches of trade and scientific literature and diagnostics industry news websites to reveal key investors and organisations in the HPV field. Bibliographic searches aided detailed mapping of these organisations, their activities and links. We collected publication data by querying the Thomson-Reuter's Web of Science (WoS) database using an *ad hoc* search string to identify those records related to HPV diagnostics.[1] This returned a sample of 1,560 scientific articles published up to 2011. Figure 5.1 depicts the number of articles related HPV diagnostics over time. The most active organisations in

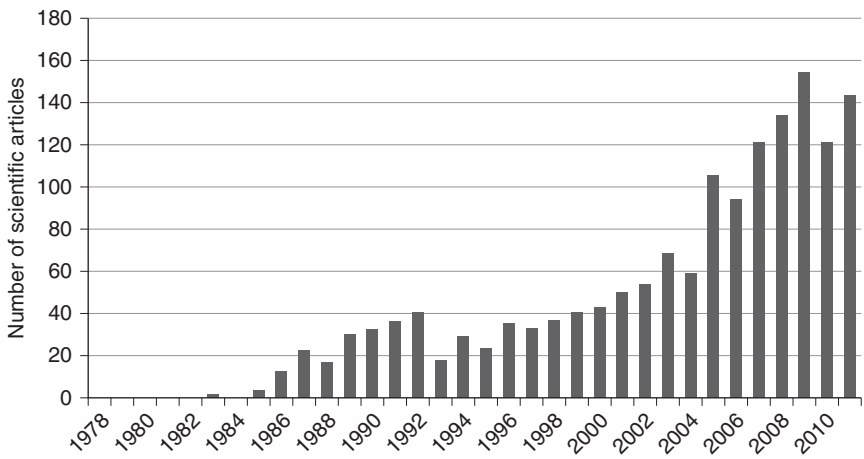

Figure 5.1 Published scientific articles related to HPV diagnostics (up to 2011).

Source: authors' elaboration on the basis of ISI Web of Science data.

Table 5.1 Top-5 profit/non-profit organisations in terms of number of published scientific articles

Non-profit organisation	*Number of publications*	*Profit organisation*	*Number of publications*
1) National Cancer Institute (NCI)	65	1) Digene (Qiagen since 2006)	35
2) Johns Hopkins University	51	2) DDL Lab	9
3) University Vrije Amsterdam	49	3) Roche	9
4) University of Turku	32	4) Abbot	5
5) McGill University	30	5) Cetus	5

Source: authors' elaboration on the basis of ISI Web of Science data.

terms of published scientific articles are reported in Table 5.1. We distinguished these organisations as non-profit and profit.[2]

Data on patents related to HPV testing were also collected.[3] Using these data, interviewees were selected based on their involvement with developments in HPV diagnostics in the USA and EU as evidenced by authorship of major papers, patents and guidelines. Industry executives, clinical scientists, laboratory directors and physicians were interviewed, including supporters of technological options that compete with Digene's kits. A pilot study in 2008 involved 12 interviews with figures from the EU and USA; in 2013–14 this was supplemented by a further 26 interviews in the USA with industry executives, clinician-researchers, regulatory officials and government scientists. 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, and we also used multiple industry interviewees to triangulate view points within and between firms with a major role in the history.

The development of cervical cancer screening in the USA

To put the adoption of HPV testing in context, it is important to understand the origin of CCS, the Pap test and the potential niches that HPV testing might occupy.

The emergence of early detection as a public health goal

The annual Pap smear test has made cervical cancer screening a cornerstone of preventive health practices in the USA. However, women were being encouraged to have regular pelvic examinations decades before the Pap entered clinical practice. At the beginning of the twentieth century senior cancer surgeons became convinced that the earlier cancer could be treated, then the greater the likelihood

that treatment might be successful (Lowy 2011). In 1913 doctors founded the American Society for the Control of Cancer (ASCC), with the primary goal to promote the benefits of early detection to physicians and the public (Gardner 2006, pp. 20–25). Although campaigners were promoting a generalised message of cancer control, the examples used were generally female cancers – breast or uterus. By the 1930s the importance of annual vaginal examinations was being promoted by women's organisations such as the YWCA, who equipped a number of health centres with facilities to conduct examinations. During the 1930s and '40s government agencies such as the National Cancer Institute and the US Public Health Service took up the cause of early intervention. It was in this context that new screening tools came to be of interest (Casper and Clarke 1998; Lowy 2011).

The development of the Pap smear

George Papanicolaou developed the Pap smear in the Department of Anatomy at Cornell University, initially through research on the menstrual cycle of guinea pigs. In 1917 he published a paper demonstrating that the microscopic examination of cervical cells collected by his vaginal smear method could be used to identify stages of the oestrus cycle. Papanicolaou then turned his attention to humans. Having demonstrated the applicability of the technique as a metric of the oestrus cycle in women, he began collecting specimens from women suffering various gynaecological conditions. Papanicolaou discovered that nearly all the specimens from cervical cancer cases contained cells that could be identified as abnormal. He published his findings in 1928, but was so discouraged by the negative response of the pathology community that a decade passed before Papanicolaou resumed work applying his smear technique to cancer detection, this time in collaboration with Herbert Traut, a pathologist at Cornell's gynaecology department. They published their first paper in 1941 and, by 1948, the technique was gaining institutional support: the National Institutes of Health began funding large-scale studies on cervical cancer screening using the Pap smear, and the American Cancer Society and the US Public Health Service financed training courses for pathologists. The process of pathology professionalisation was given institutional structure in 1951 when the Inter-Society Cytology Council (ISCC) was established. By the 1960s the Pap smear was widely available to women in the USA.

The Pap smear exemplifies a technology both deeply entrenched in medical practice and highly unstable; from its earliest clinical adoption in the 1940s, the Pap was subject to repeated modification, including changes to the labour process, the technology, the classification systems and the governance regimes that ensure its safety and effectiveness. Casper and Clarke's (1998) seminal account of Pap testing in the USA described how it has had to be 'massaged and manipulated' to transform it into a reasonably 'right tool' for cervical cancer screening. 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

Table 5.2 Three possible roles for HPV testing in cervical cancer screening

Testing protocol	*Description*
ASC-US triage (reflex)	Cytology remains screening test, HPV used only for follow-up in case of ambiguous smear test (ASC-US), reducing need for colposcopy.
Co-testing	Cytology and HPV used as joint screening tests, allowing less frequent screening for women who test negative for both tests.
HPV screening	HPV used as screening test, cytology used as a follow-up for HPV-positive women.

Source: developed by authors from primary material.

described as 'the most effective screening test for cancer that has ever been devised' (Dehn *et al*. 2007). But, with 15–50 per cent 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 visual acumen of cervical cytologists remains central to cervical cancer screening, despite protracted and expensive attempts to replace or automate the process (Casper and Clark 1998; Keating and Cambrosio 2003). Alternative methods include screening colposcopy, visual inspection with acetic acid (VIA) or with Lugol's iodine (VILI), real-time imaging and tumour markers - yet it is cytology that is synonymous with cervical cancer screening. However, this chapter focuses on the mounting pressure on cytology from a new molecular diagnostic technology: DNA tests for Human Papillomavirus (HPV) infections associated with the onset of cervical cancer.

HPV testing has already moved from its initial niche as a triage test for ambiguous cytology results, to a more central role in co-testing (i.e. used together with cytology), but in the future it could supplant the established technology (see Table 5.2). To understand the technological trajectory of the HPV test, we also chart how technological innovation *within* cervical cytology has maintained the dominance of the entrenched socio-technical regime.

The career of the HPV test

The dynamics of technological innovation can be followed longitudinally using Blume's concept of the *career*, a sequence of milestones and phases that are (i) exploration, (ii) development, (iii) adoption, and (iv) growth (Blume 1992). Building on this approach we identified the key events that shaped the emergence of HPV diagnostics and clustered them according to Blume's four phases (see Table 5.3).

Exploration (1983–1990)

In the 1980s Professor Harald zur Hausen's team at the German Cancer Research Centre discovered an association between HPV type 16 and cervical cancer

Table 5.3 Key events in the emergence of the HPV testing in the USA

Phase	*Period*	*Event*
Exploration	1972-1983	zur Hausen and Meisels separately hypothesise association between the HPV infections and cervical cancers.
		zur Hausen and colleagues clone HPV 16 in 1983.
	mid-1980s	BRL-Life Technologies (BRL-LT), in collaboration with Georgetown University, begin development of a commercial HPV test.
		Attila Lorincz (BRL-LT) and George Roth (Institut Pasteur) discover novel oncogenic HPV types which they then patent.
	1988	BRL-LT becomes the first company to gain the FDA approval for an HPV test: Virapap.
	1989	Cetus patent HPV PCR primer set.
	1990	Lack of clinical uptake leads BRL-LT to sell its diagnostic division to Digene.
	1991	Roche acquire Cetus PCR technology.
	1992	Digene develops and patents a new test called Hybrid Capture (HC). Digene begin to collaborate on a series of clinical studies in collaboration with charities, government departments, universities, and research institutes across the world.
Development	1996	Oncor gains conditional FDA approval for HPV test.
		FDA approve first Liquid-Based Cytology test (owned by Cytyc). Cytyc and Digene form alliance for development and marketing.
	1998	Ventana acquire Oncor HPV test (and related technologies).
	1999	Digene gains FDA approval for the adoption of its second-generation test (Hybrid Capture II) in ASC-US triage testing protocol.
	2001	Data from NCI-funded ALTS trials (for which Digene provided supplies free of charge) generates support for view that HPV testing is best option for AS-CUS triage, supported by the American Society for Colposcopy and Cervical Pathology (ASCCP) in new clinical guidelines.
Adoption		Digene is involved in a series of patent litigations against various rivals (Gen-Probe, Roche, Beckman Coulter, and Third Wave). The litigation ends in 2009.
	2002	Cytyc announce intention to acquire Digene but is blocked by Federal Trade Commission.
		HPV testing is included in new guidelines issued by the American Cancer Society (ACS) as an adjunctive screen in women over 30 (also known as co-testing).
	2003	FDA approve Hybrid Capture II for co-testing.
	2004	Digene rivals receive FDA warning letters for marketing tests without approval.
	2007	Qiagen acquire Digene.
		Hologic acquire Cytyc.
Growth	2008	Hologic acquire Third Wave and Roche acquire Ventana.
	2009	Hologic become second company to gain FDA approval for HPV test.
		FDA issue draft guidance on HPV test approval.
	2011	Roche and Gen-Probe gain FDA approval for their HPV tests.
	2012	New guidelines from ACS, ASCCP, ACOG and USPSTF endorse HPV testing.
	2014	Roche gain approval for use of COBAS test as primary screening tool.

Source: authors' elaboration.

(zur Hausen 1987). Their viral model of cervical cancer aetiology would in time be rewarded with a Nobel Prize, but was initially highly controversial.

The origins of this discovery begin in the late nineteenth century, when a correlation was drawn between cervical cancer, marriage and childbirth, but at this time physicians were still working with an aetiological model of cancer as the product of chronic irritation (Lowy 2011, p. 131). After the Second World War this theory was gradually replaced by an aetiology that focused on cell mutation. This new theory supported an alternative explanation of the genesis of cervical cancer: a sexually transmitted infection (STI). Despite some promising research in the early twentieth century the viral model of cancer aetiology was largely neglected until the discovery of links between viruses and some of the rarer cancers in the 1960s (Lowy 2010, pp. 137–8). The search for a viral cause of cervical cancer initially focused on herpes simplex virus and cytomegalovirus but, in 1976, papers by zur Hausen and by Meisels and Fortin identified a link between the disease and papillomavirus. The preceding year the first international papillomavirus meeting was convened by researchers from the Institut Pasteur signalling the beginnings of a new research domain. However, the significant growth of this field awaited confirmation of the viral theory which, in turn, required the development of new molecular technologies for cloning HPV types. HPV research thus became intertwined with the emergence of new technologies based on recombinant DNA and the development of the molecular diagnostics sector.

The first wave of HPV tests

Within 18 months of zur Hausen's discovery, researchers at laboratory-supplier Bethesda Research Laboratories-Life Technologies (BRL-LT) in Maryland began work on a commercial HPV test, the firm's first foray into clinical diagnostics. The BRL-LT team, led by Attila Lorincz, were fortunate to be located close to one of the pioneering HPV research groups based at Georgetown University: Robert Kuman, a gynaecologic oncologist and pathologist; Wayne Lancaster, a molecular biologist and Ben Jensen, a pathologist with training in virology. Initially BRL-LT'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 the cervical cancer samples from Georgetown were not infected with these known high-risk HPV types. Thus Lorincz's team and their collaborators at Georgetown turned to identifying novel HPV types, discovering and cloning a number of high-risk strains. This work established Lorincz as a leading figure in the nascent field of HPV research.

From the outset the commercial development of the HPV test required the creation of inter-organisational links with academics and clinicians enmeshed in the established regime of cytology-based cervical cancer screening. BRL-LT'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 BRL-LT and their academic counterparts illustrates how the commercialisation of biomedical

research has become entrenched in the practices and values of public institutions.

BRL-LT were not alone in exploring the commercial potential of HPV testing in the 1980s. Their US rivals included two first-generation biotechnology firms established in the 1970s: Cetus Corporation and Enzo Biochem (the latter formed in 1976, the same year that Bethesda Research Laboratories was established) and a wave of newer companies, including Digene, Oncor and Vysis. At the time, the fledgling molecular diagnostics sector was expanding rapidly and infectious disease tests – viral and bacterial – were the main driver of that growth.

During this period the most significant technological breakthrough in the emergent field of DNA-based diagnostics was the invention of Polymerase Chain Reaction (PCR) in 1983 by Kary Mullis, a scientist based at Cetus. PCR would become a key platform technology for the molecular diagnostics sector, broadly licensed to multiple firms and used both as a research tool and in clinical diagnostics. Within Cetus, PCR was being applied to HPV detection by a researcher named Michelle Manos and in 1989 this technology was patented as the MY09-MY11 primer set (Manos *et al*. 1989). Cetus facilitated adoption of the new technology by the HPV research community, offering training courses and providing free reagents, and PCR was rapidly adopted – the first publication using the technique came out in 1988 (Shibata *et al*. 1988) and in the same year a number of other scientists were presenting research findings based on their use of PCR techniques at the seventh International Papillomavirus conference.

1988 also marked a major milestone for BRL-LT, as they became the first company to gain FDA approval for an HPV test: the 'ViraPap' kit. The late 1980s might have appeared to have been a propitious time to launch an alternative to the Pap smear. At the time, the Pap smear test was under critical public scrutiny following media revelations that some of the larger laboratories were offering cut-price tests by forcing their staff to read 200 slides per day, more than double the work-rate recommended as safe by the American Society of Cytotechnology (Casper and Clarke 1998). Congress responded by developing new legislation to enforce more rigorous quality assurance mechanisms. However, despite some clinical uptake of ViraPap, regulatory approval proved to be no guarantee of commercial success. This was in part due to the kit's technical limitations - it was radioactive, so had a short shelf life, and was potentially hazardous to lab staff. Furthermore, it was not able to detect a sufficient range of HPV types (of which many were still being discovered). Perhaps more significant than these technical limitations was the lack of clinical data demonstrating that the test benefited patients. Some clinical experts anticipated that adoption was likely to follow once more data was available, but others expressed profound scepticism about the utility of HPV testing (Corliss 1990). The main technological change occurring in cervical cancer screening at this time was not adoption of molecular technology but a more low-tech switch in specimen collection device, from the traditional swabs and spatulas to new endocervical brooms and brush/spatula combinations (Titus 2006). Frustrated at the commercial failure of their foray into cancer screening, BRL-LT sold their molecular diagnostics division for $3.6m to

Digene, a small local rival that had recently been acquired by two entrepreneurs: Charles Fleischman and Evan Jones.

Development (1990–1999)

In a recent historical overview of the HPV research enterprise, Harald zur Hausen summarised the state of scientific knowledge in 1990:

> experimental data indicated already at that time that viral gene expression of latently infected cervical cancer cells is a necessary precondition for growth properties and malignant phenotype of these cells.
>
> (zur Hausen 2006, p.iii.)

However, according to the British scientist Julian Peto, at this stage the views of the HPV research community were not widely shared:

> It was clear to everybody who was interested in HPV by about 1985 or 1986, that this was the cause of cervical cancer. It took us ten years to persuade the rest of the world, and a lot of clinicians were sceptical until quite recently.
>
> (Quoted in Reynolds and Tansey 2009, p.49.)

The doubts raised about the utility of BRL-LT's ViraPap test were thus symptomatic of a broader scepticism at the beginning of the 1990s. As a clinical intervention and as a scientific theory HPV's role in cervical cancer had yet to gain broad acceptance in the USA. However, much would change in this decade. The second phase in the technological trajectory of HPV testing was marked by two key developments: the emergence of an international consensus that high-risk HPV infections, particularly HPV 16 and 18, were a necessary cause of cervical cancer; and growing support for the view that HPV testing could play some role in cervical cancer screening.

Underpinning these developments were two increasingly divergent strands of research: large-scale epidemiologic studies exploring the prevalence of different HPV types and their association with cervical cancer; and clinical studies examining the utility of HPV testing in cervical cancer screening. The clinical research activity was primarily conducted using a new proprietary HPV technology developed by Digene, who emerged in this period as the dominant commercial actor in the embryonic HPV testing market and the only company whose primary focus was HPV testing, while the epidemiological studies generally used PCR. Some of this work was done using the PCR primers developed by Cetus, but the major global research effort led by the International Agency for Research on Cancer chose an alternative set of primers developed in the Netherlands.

This decade saw some of Digene's rivals from the 1980s, such as Oncor and Cetus, fall by the wayside, their assets acquired by other firms. This process of industry churn led to the emergence of new player: Roche Molecular, formed in 1991 as a subdivision of the large Swiss pharmaceutical and diagnostic firm,

Hoffman-la-Roche, when the firm acquired the IP rights to PCR from Cetus (as well as many of the staff from the Cetus PCR group). Michelle Manos, who had led the HPV PCR development at Cetus, did not join Roche Molecular. One reason may have been that the Cetus management who joined Roche did not think HPV was a priority. According to one former Cetus employee, even before the Roche acquisition, Cetus management had taken the view that HPV testing was 'like a fine wine' (USA 25), something that needed time to mature:

> The general consensus was … we'll let Hybrid Capture spend the money to develop the market and then if that comes out to be something important, we could develop the test quickly and go and take over ….
>
> (USA 25.)

Instead, Roche devoted much of its resources to HIV diagnostics, where there was a rapid growth in viral load testing for prognosis and monitoring of patients. However, the firm retained a presence in HPV research during the 1990s by continuing the Cetus practice of giving scientists free PCR reagents.

Oncor was another potential rival and, unlike Roche, Oncor were committed to HPV testing in the early 1990s, gaining conditional FDA approval for their test in 1996. However, in 1996 Oncor decided that it needed to reconfigure the test 'to facilitate automation and integration of the test with automated Pap Smear testing' (Yuxiang (for Oncor) 1996). Oncor stated that this would entail both a new approval application to the FDA and developing a cooperative agreement with one of the firms manufacturing automated cytology. However, before the firm was able to do this, it ran into multiple difficulties: patent litigation with a rival company forced it to withdraw many of its products from the market and, by October 1998, its financial problems were so severe that trading on its stock was suspended. In an effort to generate cash, it sold its HPV test and related products to Ventana in 1998. Oncor's failure arose in part because of the breadth of its pipeline - much of its R&D activity in the mid-1990s was focused on gaining FDA approval for its Her-2/neu test. According to one former employee the combination of the cost of this process and the loss of revenues arising from the patent litigation meant that Oncor 'didn't really have the wherewithal to do the kind of stuff that ultimately was required to get HPV commercialised' (USA 21). According to a report in the *Washington Post*, Oncor's HPV failure was symptomatic of a broader problem within the company:

> A widely held view among present and former Oncor employees is that the company tried to do too much, too fast, spending its energies and precious capital on a slew of endeavors without focusing on any one of them long enough to make a business out of it.
>
> (Gillis 1998.)

Even at Digene the future of HPV testing (and thus its value as a focal point for the firm's R&D efforts) was the subject of internal debate within the company, a

debate that would only be fully resolved in the mid-1990s as the company prepared for its public flotation. The initial focus of the firm was to develop a new platform technology, which might support a range of tests, as Cetus had done with PCR.

Developing the HPV testing technology

The new platform, called Hybrid Capture (HC), was already in development at BRL-LT in the late 1980s, and was patented by Digene in 1992. It was a non-radioactive method for detecting specific HPV strains by hybridising HPV DNA from clinical samples with complementary RNA sequences in the kit that annealed together forming the detectable 'hybrid' molecule. Detection of HPV was achieved via antibodies that 'captured' the DNA-RNA hybrids created from an HPV-infected sample. Digene's HC test was more specific than rival PCR-based tests that were seen as too sensitive for clinical use (Poljak *et al*. 1999).

However, the HC was not simply a technically superior assay; as Digene's patent-protected proprietary platform it embodied a strategy of technological autarky. Many molecular diagnostics companies produce reagents that can be run on the platforms of their commercial competitors, 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 […]' (a Digene executive).

The creation of a proprietary platform technology was a commercial advantage whatever HC was used for but, in the HPV market, Digene sought more than simply independence from rival firms through *platform* patents; it wanted to create a barrier to market entry through *biomarker* patents. HC was designed to identify ten high-risk HPV types, and Digene had patented or exclusively licensed five of those types for diagnostic use in the USA. They extended their legal monopoly with the second-generation version of HC, which contained three more HPV types, of which one was exclusively licensed to Digene.

Demonstrating clinical utility

The clinical scepticism that had greeted BRL-LT's ViraPap in 1988 was sufficient to suggest that a superior assay protected by platform and biomarker patents was no guarantee of commercial success; market acceptance would require robust evidence that demonstrated the clinical value of HPV testing in cervical cancer screening. To that end, Digene participated in multiple large head-to-head clinical studies against the Pap test during the 1990s, in collaborations with charities, government departments, universities and research institutes across the world. The clinical evidence base for their test grew incrementally, but was still limited when the first-generation Hybrid Capture test gained FDA approval in 1995. However, by 2003 Digene claimed that it had participated in studies involving 'an aggregate of approximately 90,000 women on four continents' (Digene 2002, p. 12) and the

firm had increased their annual R&D expenditure to $10.6m per year. A significant portion of this sum was spent on platform development and on extending the range of tests the company offered on the platform. Nevertheless, Digene was putting some of its money into HPV clinical studies – estimated at somewhere between $20–30m in the 1990s (a former Digene executive). This level of investment was unusual; diagnostics companies have not traditionally invested significant sums to demonstrate the clinical validity and utility of new biomarkers.

Using the data collected from ISI WoS (see the Methods section), an exploratory analysis of Digene's co-authorships in scientific articles reveals how this R&D programme placed the firm at the centre of a global research network. Figure 5.2 depicts Digene's ego-network dynamics[4] across a series of three-year time windows. While Digene's ego-network clearly grows over time, the strong inter-organisational links with the National Cancer Institute, Johns Hopkins University and Kaiser Permanente are particularly evident, with repeated publications within and across time periods. Digene collaborated with the private healthcare system Kaiser Permanente and the National Cancer Institute on two studies crucial to adoption of the HC2 test for use in ASC-US triage.

As suggested earlier, this clinical research activity was distinct from the more strictly epidemiological studies that were focused on the prevalence of different HPV types and their causative association with cervical cancer. Progress in this strand of research was a prerequisite for acceptance of HPV as the necessary cause of cervical cancer in the wider scientific and clinical communities beyond the growing HPV research community. Two major milestones in this regard came mid-decade: a 1995 paper by Bosch *et al*. reported the findings of the International Biological Study on Cervical Cancer (IBSCC), a transnational study spanning 22 countries, which found that HPV was present in 93 per cent of invasive cervical cancer samples. Official recognition of their findings came when the International Agency for Research on Cancer declared HPV 16 and 18 (the two most prevalent high-risk HPV strains) to be carcinogenic agents (IARC 1995).

Mid-decade was a significant period for Digene as well. In preparation for its public flotation the company was advised by its bankers that it would not have strong appeal to investors if it presented itself as a broad-based molecular diagnostics company. Two other diagnostics companies had recently successfully floated, branding themselves as women's health companies, and Digene's advisers recommended that they ride two investment bandwagons at once - women's health and DNA - by focusing on HPV as their lead product. This external guidance resolved the firm's internal debate about the relative importance of the HPV test as its principal focus.

In 1999 Digene gained FDA approval for use of the HC2 test in ASC-US triage. At this stage the firm was taking a cautious approach to molecularisation of cervical cancer screening in the US market, seeking to support rather than supplant the Pap test. FDA approval of Hybrid Capture 2 marks the end of the development phase for Digene's technology (although earlier HPV tests for HPV testing such as BLT's had already passed the development phase but failed in the market).

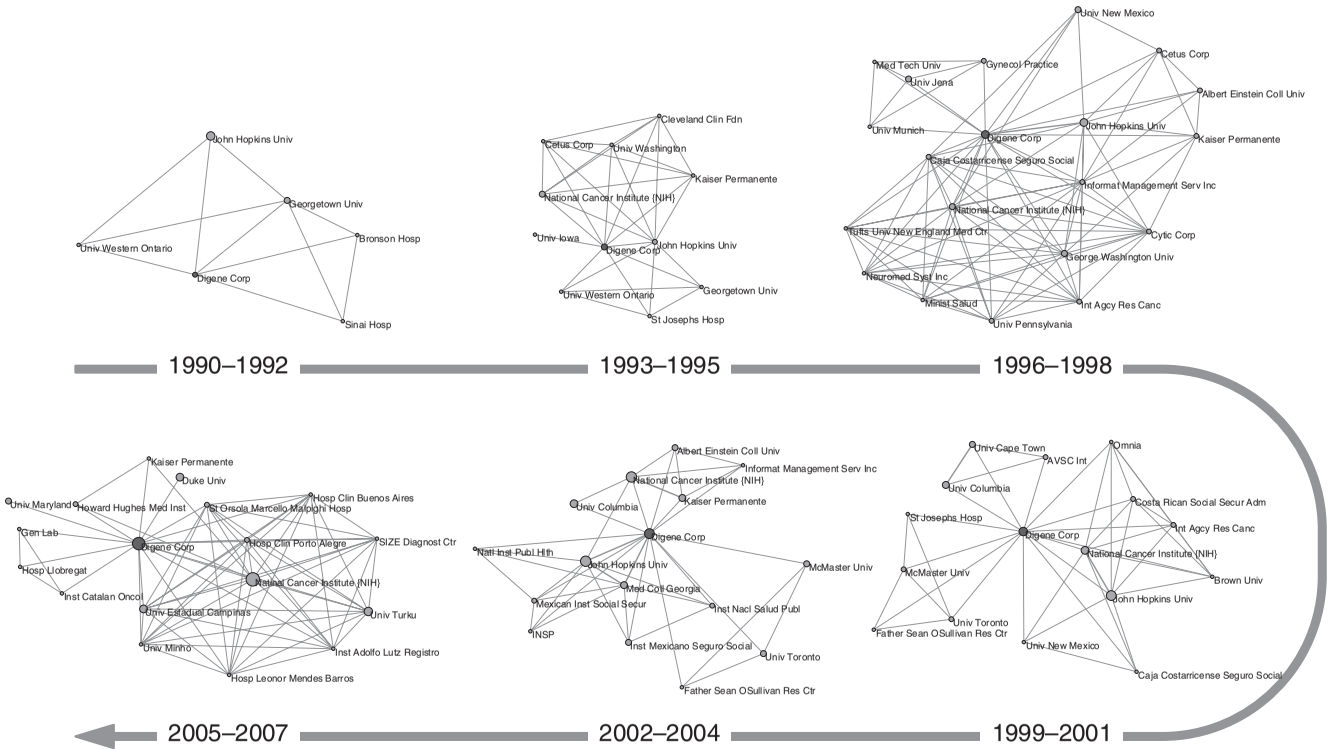

Figure 5.2 Digene's ego-network dynamics (co-authorship network). The size of nodes is proportional to the number of scientific articles related to HPV diagnostics that the given actor published in the relative time window.

Source: authors' elaboration on the basis of ISI Web of Science data and by using the Pajek software package.

FDA approval was a major milestone in the strand of HPV research focused on demonstrating the clinical utility of HPV testing, but 1999 also marked the final confirmation of the epidemiological investigation of the role of HPV in cervical cancer. Researchers in the global IBSCC study had reanalysed their HPV negative samples on the assumption that the 93 per cent prevalence rate they had reported in 1995 was lower than the true prevalence, probably as a result of inadequate specimens or HPV DNA integration. On reanalysis they found that the prevalence of HPV in their cervical cancer specimens was 99.7 per cent. They published their new findings in the *Journal of Pathology* with the bold and simple title: 'Human Papillomavirus is a necessary cause of cervical cancer worldwide' (Walboomers, *et al*. 1999). The concluding paragraph emphasised the scientific significance of the finding: 'this would indicate the highest worldwide attributable fraction ever identified for a specific cause of a major human cancer' and its clinical implications: 'our results reinforce the rationale for HPV testing in combination with, or even instead of, cytology in population-based screening programmes' (Walboomers *et al*. 1999, p. 18).

Adoption 1999–2003

Leading figures in the global HPV research community may have been making bold claims that HPV testing could replace the Pap smear but, in 1999, it was not clear whether Digene could build a sustainable market for their test in the modest role of ASC-US triage. However, by 2003 HC2 was becoming established in cervical cancer screening in the USA, Digene was nearing profitability, and commercial rivals were entering the market with their own HPV tests.

Early adoption of the first version of HC occurred even before FDA approval of HC2 in 1999, but gained a subsequent boost from new publications supporting use of the second-generation test, including a study Digene had funded with Kaiser Permanente (a large US healthcare provider) and the NCI's ALTS data. The ALTS trial was a major $21m study funded by the National Cancer Institute for which Digene provided test kits free of charge. The ALTS data was not part of the evidence submitted to FDA for approval of HC2 as the trial was still ongoing, but it is widely regarded as crucial for the subsequent endorsement of the test by professional bodies.

The commercial failure of the ViraPap had demonstrated that FDA approval was not necessarily sufficient to gain clinical adoption; overcoming clinical resistance would require backing from leading clinicians and scientists, and in the contemporary healthcare system the most effective form of professional validation is endorsement in a clinical guideline. In the last two decades the emergence of evidence-based medicine (EBM) has fuelled the growing importance of clinical practice guidelines. It has been estimated that 1,000 new guidelines are produced each year in the USA (Timmermans and Berg 2003, p. 7).

The first professional endorsement came from the American Society for Colposcopy and Cervical Pathology (ASCCP). The 2001 ASCCP guidelines stated that (providing a suitable sample was collected with the initial Pap test)

HPV testing was the preferred way of triaging women with AS-CUS, although the established options of repeat cytology or immediate colposcopy were also acceptable. The opening section of the guidelines noted that there was evidence to suggest that, in combination, the new technologies of HPV testing and liquid-based cytology 'are attractive alternatives for managing women with certain types of cytological abnormalities' (Wright *et al*. 2002, p. 2120). The guidelines presented three options: repeat cytology, colposcopy and reflex HPV testing. Reflex testing with HPV was presented as overcoming many of the disadvantages of the first two options: it did not require taking an additional specimen and would reduce the number of women referred to colposcopy by 40–60 per cent. Data from the ALTS trial is considered by many to have been critical to the guidelines:

> It [the ALTS trial] validated the performance of the test … and the recommendations based on that through ASCCP pretty much directed the growth of that test.
>
> (US LAB 2.)

The ASCCP guidelines also illustrate how Digene's network of collaborators were now playing a critical role as advocates for clinical adoption of HC2. Among 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, including Tom Wright, the lead author. Similarly, five of the 38 working group members for the ACS guidelines disclosed some link to Digene.

The influence of Digene's network of collaborators is further demonstrated by an editorial, which accompanied the 2001 ASCCP guidelines, written by Mark Stoler, a senior expert in cytopathology and a participant in the ALTS trial. While the guidelines only stipulated that testing should be done 'using a sensitive molecular test', Stoler's editorial asserted that because the guidelines only drew on evidence from studies that used Digene's HC2 test, this was now the *de facto* standard for HPV testing (Stoler 2001).

Digene now 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 increased their 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 (from personal communication with US venture capitalist, August 2006). This was a significant break with tradition: 'In contrast to pharmaceutical manufacturers, neither test manufacturers nor laboratory service providers generally have large, sophisticated marketing teams targeting physicians, health plans and patients' (Ramsey *et al*. 2006, p. 198).

By 2003 Digene had gained near universal insurance coverage for use of its test in ASCUS triage, acquired 62 per cent of the potential AS-CUS triage market

in the USA, its customers included all the major US reference laboratories, and the company had finally become profitable. Digene's successful creation of a market for HPV testing in the USA piqued the interest of its commercial rivals. Using the technology it had acquired from Oncor, Ventana launched an IHC test in 2001 (without FDA approval). Senior management at Roche began to pay more attention to HPV testing around 1999, their interest sparked by the clinical data from the Kaiser Permanente study and the 1999 Walboomers paper that had confirmed the role of HPV as a necessary cause of cervical cancer.

However, HPV testing was not without its critics. Senior experts had criticised the early ALTS data (Herbst *et al*. 2001), and in 2003 the United States Preventive Services Task Force issued a new guideline stating that there was insufficient evidence to support use of HPV testing. Even in Kaiser Permanente, which had been a rapid early adopter of HC2, there were sceptics. Kaiser's HPV advocates were based in its Northern California division but, in Southern California, Neal Lonky and colleagues published a study of HPV-based ASC-US triage in 2003, concluding that the sensitivity of HC2 was a cause for concern:

> Although less complicated than colposcopy, the Hybrid Capture II triage algorithm for ASCUS will under-diagnose some women with high-grade CIN, when compared with colposcopy.
>
> (Lonky *et al*. 2003.)

The final critical development to note in this period was not a molecular HPV test but a refinement of the Pap smear: Liquid Based Cytology (LBC). The leading manufacturer of LBC kits was a US firm called Cytyc, which had first gained FDA approval for their ThinPrep test in 1996 (the same year in which the ALTS trial began). Its chief commercial rival AutoCyte had its SurePath test approved by FDA in 1999. Clinical adoption of LBC grew rapidly following the publication in 1999 of a study of the new technology carried out by Quest, one of the two major US reference laboratories. FDA approval of the Digene test was based on sample collection using either Digene's proprietary collection kit and preservation medium or using Cytyc's technology (that, to date, the FDA has not approved). The two firms had collaborated on the ALTS trial and in 2001 Digene and Cytyc announced that they would embark on a joint promotion campaign for their respective products (Anonymous 2001). Cytyc even planned to acquire Digene, but the Federal Trade Commission blocked the transaction.

Growth (2003–2014)

Following adoption of HC2 for triage, Digene focused on the larger screening market. Since 2003, growing sales, the market entry of other companies, and endorsement in new clinical guidelines demonstrate widespread validation of HPV testing. In 2014 FDA approval of Roche's COBAS HPV test for use as the sole primary screening test, has created the possibility that cytology may lose its primacy in cervical cancer screening.

Digene's strategy to expand its market

Use of Digene's test for triage of AS-CUS cases was the low-hanging fruit of HPV testing. It exploited a chief clinical weakness of cytology, namely the large number of ambiguous results requiring further follow-up, but did not challenge cytology's status as the gold standard for cervical cancer screening. ASCUS triage 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 cytology or an alternative to it. The company's intent was made clear in an article in the *Washington Post* in January 2001 in which Evan Jones, Digene's CEO and chairman, stated: 'Our goal is to replace the Pap smear' (Chea 2001). However, at this stage there was scepticism even among leading figures in Digene's network of collaborators; the same news report quoted the NCI's Mark Schiffman expressing caution about a shift away from cytology: 'The Pap smear has a long tradition of reducing cervical cancer… We don't want to dislodge good cervical cancer screening unnecessarily'. Adjunct screening, also known as co-testing, was a compromise between those advocating the use of HPV testing as the sole primary screening test and influential figures like Schiffman who were more cautious.

In 2002 guidelines from the American Cancer Society (ACS) recommended HPV testing as an adjunctive screen in women over 30, and in 2003 this indication gained FDA approval and clinical endorsement in a guideline from the American College of Obstetricians and Gynecologists (ACOG 2003). The adjunct screening version of the Hybrid Capture test was branded as DNAwith Pap. By 2003 the company had increased its annual HPV testing revenue 64 per cent to $40m and it estimated that the approval for co-testing had created a potential market for its product of $400m. Its 2003 annual report stated that it had achieved insurance coverage for more than 50 million lives for co-testing.

Long-time Digene collaborators Kaiser Permanente were early adopters, again demonstrating the importance of key inter-organisational links (such as the research collaborations indicated in Figure 5.1), 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.)

Even in the organisational structure of Kaiser Permanente, implementation of this new testing protocol met with initial clinical resistance (despite an educational

programme to persuade clinicians of its virtues), and elsewhere clinician adoption was slow. The advantage claimed for the combined screening technologies was that women with negative results need not be tested again for three years (in the USA annual screening is routine). But lengthened intervals was a significant shift in practice:

> For many women, the only reason they see a clinician is to have a Papanicolaou smear taken. Although that specimen might not be necessary, many other events, critical to the maintenance of health, occur during the Papanicolaou smear visit. These include the measurement of blood pressure and weight, review of vaccinations and medications, and counselling regarding a healthy lifestyle.
>
> (Noller *et al*. 2003.)

Digene developed an multi-pronged marketing strategy for the commercial launch of DNAwithPap, including: collaborating with government agencies, professional bodies and women's advocacy groups to communicate their support for the test among professionals and the public; partnering with laboratories to co-market the test to physicians and payors; and creating demand through education programmes driven by their physician detailing organisation and independent third-party organisations to educate physicians and women about HPV testing (Digene 2003, pp. 14–15).

Digene funded Women in Government (WiG), a Washington DC-based non-governmental organisation, who launched the Challenge to Eliminate Cervical Cancer Campaign in 2004. Women in Government targeted state policymakers with the message that cervical cancer was preventable and that 'all women [should] have access to the most advanced and appropriate cervical cancer prevention technologies, regardless of their socioeconomic status'. By 2006 California, Maryland, North Carolina, New Mexico, Texas and Virginia had amended their legislation to mandate coverage of HPV testing. Other NGOs working with Digene included the Coalition of Labour Union Women, Hadassah (the Women's Zionist Organisation of America) and the Women's National Basketball Federation. Digene even had a musical campaign, the Pop Smear tours organised by Yellow Umbrella and led by Christine Baze, a musician and cervical cancer survivor.

However, despite a promising level of early adoption in the first 18 months after FDA approval, growth began to stall thereafter. Digene responded by adopting a new marketing strategy: direct-to-consumer advertising. The company reported that it planned to spend between $3–5m in 2005 on adverts on television and in women's magazines, which carried stark messages such as 'You're not failing your Pap test, but it might be failing you' (Grebow 2005). A report in the *Washington Post* highlighted professional disquiet with the campaign; Marcia Angell, a former editor of the *NEJM*, suggested that the ads '…were just trying to frighten women' and questioned the legitimacy of DTC advertising: 'It's marketing, and it creates demands that should just be between patients and their doctors' (Rosenwald 2005). Digene defended its advertising campaign as a legitimate

educational tool that raised women's awareness of the cause of cervical cancer. A consumer survey conducted six months after launch of the campaign found that '82 per cent of women exposed to the ads said they had talked or planned to talk with their doctors about the HPV test … [and that] 51 per cent of physicians surveyed said they had seen a significant increase in requests for the HPV test'. Perhaps, most tellingly, while test revenues increased 42 per cent over the six-month period in the USA as a whole, growth was 85 to 115 per cent in the metropolitan areas, which had been targets for both print and TV ads (Luchtefeld 2006).

A molecular monopoly - protecting market share

Despite continuing clinical resistance the HPV market has grown. Most insurance companies cover HPV testing; it is mandated under the Affordable Care Act for women 30 or over as a service that insurers must provide without charging women copayment fees, and is available through the public Medicaid system in most states. In 2008 industry estimates suggested that more than 10 million tests were being performed annually and that the market had grown 40 per cent in each of the past five years (Fischer 2008). Yet at the end of the fiscal year for 2006, Digene estimated their penetration of the total potential US HPV testing market to be approximately 18 per cent. In 2007 an industry news report quoted Roche Molecular as stating that the co-testing market had reached 20 per cent (Bruderlin-Nelson 2007). By 2009 Qiagen (who had acquired Digene) were stating that the screening market had reached 30 per cent penetration (Clancy 2009). The figures from the laboratory at Johns Hopkins University illustrate how much more slowly the contesting market grew compared with ASCUS triage.

Furthermore, despite being the only FDA approved test until 2009, not all HPV testing was performed using Digene's HC2. Some pathology labs were developing their own tests from component reagents sold by other firms The FDA had long permitted diagnostics companies some latitude, permitting them to sell what it termed Analyte Specific Reagents (ASRs) to laboratories without regulatory approval, providing the firm made no marketing claims and gave no instructions for use. Responsibility for validation of tests developed using ASRs thus falls on the laboratories, rather than the diagnostics firms, and laboratories must report test results with a disclaimer noting that the test has not been FDA-approved. By 2004 the ASR rule was being exploited by a number of firms marketing HPV ASRs including Roche, Third Wave and Ventana. However, in 2004, both Ventana and Roche received communications from the FDA stating that their HPV ASRs would require pre-market authorisation as Class III devices. Roche removed their products from the market and sought FDA approval, but Ventana was permitted to keep its ASRs on the market subject to changes to its product literature (Anonymous 2004). A 2006 survey suggested that other tests were being used in 19.1 per cent of US labs, either alongside Digene's HC2 test, or instead of it (Moriarty *et al*. 2008).

Regulatory approval was only a partial barrier to market entry but Digene also benefited from interventions by their collaborators to limit the spread of rival

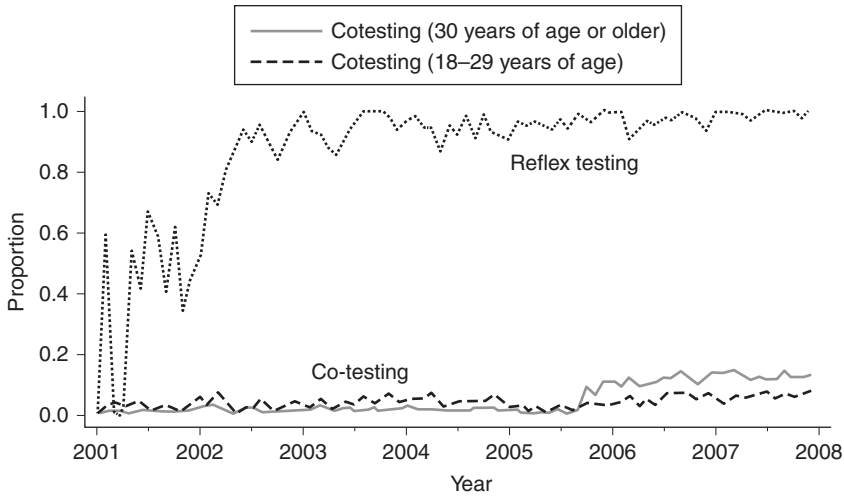

Figure 5.3 Monthly proportions of human papillomavirus (HPV) reflex testing and co-testing with Pap for Pap specimens processed by the Johns Hopkins Hospital Division of Cytopathology, 2001–2007.

Source: Phelan, 'Trends of human papillomavirus testing'. *Obstet Gynecol* 2011.

technologies lacking FDA approval. Controversy about such tests was raised in 2005 in an article in *CAP Today*, the magazine of the College of American Pathologists, which 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 Atilla Lorincz, Digene's Chief Scientific Officer: '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'.

This position was reinforced by the endorsement of HC2 in clinical guidelines. The 2002 ACS guidelines that recommended co-testing stated that HC2 was the only test approved by FDA and that only evidence from studies using HC2 had been used in the development of the guidelines. In 2006 new ASCCP guidelines went further, suggesting less validated tests 'may increase the potential for patient harm' (Wright *et al*. 2007, p. 347). These statements reinforced the status of Hybrid Capture as the gold standard for HPV testing. Thus two forms of gate-keeping – statutory licensing and professional self-regulation – were mutually reinforcing: the guidelines affirmed the importance of FDA approval, and the status of Digene's

HC2 test as the only FDA-approved test legitimated the focus on the company's proprietary technology within the guidelines. The guideline authors stressed the need for HPV tests to be thoroughly validated and this was an implicit endorsement of FDA's position that all HPV tests should be treated as Class III, high-risk devices subject to the most rigorous PMA approval process.

Digene also sought to restrict competition by using intellectual property rights as a barrier to market entry. We have already referred to Digene's legal monopoly on key high-risk HPV strains. Between 2001 and 2009 this monopoly was defended in a series of US law suits with rivals Beckman Coulter, Gen-Probe, Roche and Third Wave.

Rivals gain FDA approval

The high bar of FDA approval and the power of Digene's patent position combined to exclude any serious competition in the US market for a decade. Roche bought the Institut Pasteur's patents (including patents on HPV types exclusively licensed to Digene) in 2002 and launched an HPV test in Europe in 2003, but the firm's attempts to gain FDA approval for its Amplicor and Linear Array HPV tests failed. Digene lacked an FDA-approved commercial rival until Third Wave gained approval for their Cervista test in 2009. Competition intensified in 2011 when the FDA approved HPV tests from Roche and Gen-Probe, the two largest molecular diagnostics companies in the USA.

Market entry by rivals to Digene was not the only signal that HPV testing was now an established market with strong growth potential - the field has also seen multiple acquisitions. In 2007 Digene was bought for $1.6bn by the German firm Qiagen, a price that 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). Hologic, a US firm with ambitions to be the leader in women's health diagnostics, has acquired both Third Wave (in 2008) and Gen-Probe (in 2012), giving it multiple HPV technologies. Hologic's acquisition of Cytyc (in 2007) has given the firm the combination of liquid-based cytology and HPV technologies, which Cytyc had sought to achieve when it tried to acquire Digene in 2002.

New guidelines converge on co-testing

The prospects for HPV testing were given a boost in 2012 with the publication of three new guidelines endorsing routine co-testing. Reflecting the new market reality of multiple FDA-approved tests, these guidelines no longer rely solely on evidence from studies using Digene's HC2 test, although they state that in the USA only FDA-approved tests should be used in clinical practice and recommend against the use of laboratory-developed tests.

These new guidelines drew on new evidence from four large randomised-control trials that had been published in the preceding five years. The US Preventive Services Task Force (USPTF) guideline summarised their evaluation

of the evidence thus: 'Modelling studies support similar benefits of co-testing every 5 years and cytology every 3 years, demonstrating small differences in expected cancer cases (7.44 *vs*. 8.50 cases, respectively) and cancer deaths (1.35 *vs*.1.55 deaths, respectively)' (Moyer 2012, p. 887).

Based on this new data the USPTF (which had previously rejected any use of HPV testing) now supports co-testing, although it does not say it is the preferred option (Moyer 2012). By contrast a joint guideline from the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology (Saslow *et al*. 2012) and a new guideline from the American College of Obstetricians and Gynaecologists (ACOG 2012) went further, both stating that for women 30 or over, co-testing is preferable to the use of cytology alone (although the preference for co-testing was classed as a 'weak' recommendation in the appendix to the ACS guidelines).

The three guidelines shared a stated aim: to reduce unnecessary screening. A common recommendation was no cervical cancer screening in women under 21, a change which could save at least $500m a year (Morioka-Douglas and Hillard 2013). For older women, the guidelines all recommended a move away from annual screening, an extension of prior attempts to lengthen screening intervals in the USA.

However, while guidelines have helped to drive clinical adoption of HPV testing, the impact of their recommendations has been uneven. We have already seen that a proportion of laboratories did not follow the recommendation to use only FDA-approved tests, and that adoption of co-testing has been slower than for ASCUS triage. Lack of physician compliance has been investigated in a number of studies. A survey of ACOG members carried out in 2011–12 found that around half were using co-testing but that most were continuing to offer annual tests: 'Physicians felt that patients were uncomfortable with extended screening intervals and were concerned that patients would not come for annual exams without concurrent Paps' (Perkins *et al*. 2013). A 2006 survey of primary care physicians found that those who would recommend co-testing were less likely to comply with guidance on lengthened screening intervals (Saraiya *et al*. 2010), suggesting that co-testing appeals to a 'more is better' mentality. In an interview Alan Waxman, one of the authors of the 2012 guidelines, discussed one of the concerns that influence physicians: 'Healthcare providers are influenced by dramatic cases they see. This is what we call the "N of 1." You see 1 bad case and you want to direct your management for all patients to fit that case' (Terry *et al*. 2013).

Our interviewees frequently suggested that persistence of annual testing is another example of the practice of defensive medicine in the USA. However, they also alluded to a number of other factors slowing adoption of co-testing and lengthened screening intervals, the chief one being feared loss of income and another being a reluctance to have to counsel patients on a positive HPV test.

Even those involved in writing the guidelines suggested that compliance was not a straightforward matter because the new system was far more complex than the established management protocols.

> the old message … Get your Pap, easy message. What's the message now? Get your pap and if abnormal, now it's get your HPV test and if you're positive, if you're negative you get into the controversy of how long to wait until doing it again, if you're positive you get into the issue of where did I get it blah-blah-blah and then if you're in because of co-testing in the US, if you have a discrepant result: HPV positive/pap negative, HPV negative/ASCUS, HPV negative/LSIL, there's all these combinations that dominate a book this size, this is a guidelines book I mean it's just too complicated ….
>
> (USA 2.)

Beyond cytology?

Notwithstanding these unresolved issues, the ACS and USPTF guidelines also point to emerging evidence that may support the use of HPV testing as the sole primary screening test. In April 2014 Roche became the first firm to win FDA approval for this indication. The experience of co-testing would suggest that such a dramatic shift in clinical practice may be extremely difficult to achieve. Although the experts on the FDA advisory committee that reviewed the Roche submission in March 2014 were unanimous in their support for approval of primary screening in women 25 or over, there was resistance from some groups, including a coalition of 17 NGOs led by the Cancer Prevention and Treatment Fund, who wrote a joint letter to Margaret Hamburg, the FDA Commissioner, arguing that the superiority of HPV primary screening is unproven: 'It replaces a safe and effective well-established screening tool and regimen that has prevented cervical cancer successfully in the U.S. with a new tool and regimen not proven to work in a large U.S. population' (Patient, Consumer and Public Health Coalition 2015).

David Chelmow, a spokesman for ACOG, expressed several reservations at the advisory committee meeting: that the new option would further confuse clinicians still struggling to come to terms with the complex management options available under the 2012 guidelines; that there was a lack of data on some of the issues which a transition to primary screening would raise, such as what to do with women under 25; and finally, the absence of data on the comparative benefits of co-testing *vs*. primary HPV screening.

Following the approval announcement, ASCCP indicated that it was working with other professional bodies on an interim guidance to address the new option (ASCCP 2014), but at the September 2014 meeting of the International Papillomavirus Society it was revealed that progress towards a new guidance is slow, with experts in disagreement on a number of issues, including the age at which to start HPV primary screening, the appropriate screening interval, and the optimal triage protocol for HPV positive women.

Conclusions

HPV testing has been available for 25 years, but it has yet to supplant cytology; instead, the molecularisation of cervical cancer screening has required an

accommodation with the established socio-technical regime. This reflects the wider picture in oncology, where diagnosis still relies on morphological examination of tumour biopsies, despite a growing number of molecular diagnostics. 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 2003, p. 426). This mirrors the uptake of biotechnology in pharmaceutical R&D, where biotechnological techniques have reinvigorated traditional small molecule drug discovery, as well as supporting the development of novel biologic therapies (Hopkins *et al*. 2007). As the historian David Edgerton has suggested, we should not mistake the first appearance of a technology for its triumphant dominance, and older technologies may be increasing in use, even as new ones are growing in popularity (Edgerton 2006, p. 31–2).

Notwithstanding these continuities, the history of HPV testing in the USA suggests that the molecularisation of cancer diagnosis is accompanied by some important changes in the diagnostic innovation process. The emergence of the Pap smear exemplified two key characteristics of diagnostic innovation in the twentieth century – publicly funded discovery and development of a new biomarker, and the creation of a new sub-specialty within the pathology profession. The Pap smear emerged from basic research conducted in an academic setting. Its potential clinical application was first explored in the 1920s during a period when pathologists were gradually wresting control of cancer diagnosis from the surgical profession (Lowy 2010, p. 20), and its development exemplified a model of diagnostic innovation in which the public sector played the primary role.

The history of laboratory diagnostics in the twentieth century was one of professionalisation and the creation of new sub-disciplines such as microbiology and radiology (Amsterdamska and Hiddinga 2003). 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.

The development of Hybrid Capture involved a dynamic process of deepening engagement between Digene and a variety of actors in the public sector. 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 that could be subject to cross-comparison and meta-analysis. Finally, as the research community began to produce findings that 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 that had both

proven its value in multiple large clinical trials and carried the imprimatur of FDA approval. Digene thus harnessed a growing interest in the clinical potential of HPV testing to create an international research network focused on demonstrating the clinical utility of their proprietary technology.

The establishment of Hybrid Capture as the tool of choice for detecting the presence of HPV was not simply a question of which company had the superior technology but was also a matter of intellectual property rights. Digene's success was achieved not only by enrolling key supporters to drive clinical adoption, but also by (at least temporarily) excluding competitors from joining the network.

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 'systems integration' role for diagnostics companies, mirroring that seen in pharmaceutical firms (Hopkins *et al*. 2007), illustrating how molecularisation involves not simply a greater role for industry but also a shift in business models. Crucial aspects of Digene's commercial strategy - patenting biomarkers to try and gain a period of market exclusivity, marketing to physicians, consumer advertising, investing heavily in studies to demonstrate the clinical utility of a test – were all relatively novel to the IVD industry, and some at least were not without controversy.

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 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. Collaboration with industry has thus reinforced the authority of the established network of public sector actors in US cancer screening.

Acknowledgement

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Notes

1 We limited the search of the keywords and their combinations to those in the titles of scientific articles. We specifically used the following search string in the WoS: (TI=HPV* or TI="Human Papilloma Virus*" or TI="Human Papillomavirus*" or TI="Human Papilloma*virus*") and (TI=Cervical or TI=Cervix) and (TI=diagnos* or TI=test* or TI=assay or TI=detect* or TI=screen* or TI=predict*). It is worth noting that while it is also possible to search the keywords in the abstracts of scientific articles, which would allow more records to be retrieved, this would increase the number of records not closely related to the HPV diagnostics (Rotolo *et al*. 2014).

2 The cleaning of organisations' names was performed by using The Vantage Point software.
3 The study required a full 'patent landscape' to reveal commercially active organisations - see Hoschar *et al*. (2007) for a description of patent search methods. Some of these results are discussed elsewhere in Hogarth *et al*. (2012) but are not reproduced here.
4 An ego-network (or ego-centred network) 'consists of a focal actor, termed ego, as set of alters who have ties to ego, and measurements of the ties among these alters' (Wassermann and Faust 1994, p. 42).

References

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

ACOG (2012) Screening for cervical cancer. Practice Bulletin No. 131. American College of Obstetricians and Gynecologists. *ObstetGynecol* 120, pp. 1222–38

Amsterdamska, O. and Hiddinga, A. (2003) 'The analyzed body' in R. Cooter and J. Pickstone (Eds) *Companion to Medicine in the Twentieth Century*. London: Routledge, pp. 417–434

Anonymous (2001) 'Cytyc and Digene announce exclusive co-promotion agreement'. *Business Wire*, 18 Jan.

Anonymous (2004) 'Ventana's HPV test retains ASR status'. *IVD Technology*, 1 June. Available online at: www.ivdtechnology.com/article/ventana per centE2 per cent80 per cent99s-hpv-test-retains-asr-status

The American Society for Colposcopy and Cervical Pathology (ASCCP) (2014) 'FDA announcement expands options for cervical cancer screening'. Maryland: ASCCP

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

Bosch, F. X., Manos, M. M., Muñoz, N., Sherman, M., Jansen, A. M., Peto, J., Schiffman, M. H., Moreno, V., Kurman, R. and Shah, K. V. (1995) 'Prevalence of human papillomavirus in cervical cancer: a worldwide perspective'. *J Natl Cancer Inst*, 87: pp. 796–802

Bruderlin-Nelson, C. (2007) 'HPV test market expected to boom'. *IVD Technology*, May

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*, 28, pp. 255–290

Chea, T. (2001) 'New cervical cancer test gains backers'. *Washington Post*, 31 January

Clancy, S. (2009) 'Inside track'. *Clinical Lab Products*, April

Corliss, J. (1990) 'Utility of ViraPap remains to be established'. *Journal of National Cancer Institute* 82(4), pp. 252–3

Cox, T. and Cuzick, J. (2006) 'HPV DNA testing in cervical cancer screening: from evidence to policies.' *Gynaecologic Oncology*, 103, pp. 8–11

Dehn, D., Torkko, K. C. and Shroyer, K. R. (2007) 'Human papillomavirus testing and molecular markers of cervical dysplasia and carcinoma'. *Cancer*, 111, 1, pp. 1–14

Digene (1996) 'S-1/A, S-1 Amendment # 3'. 21 May

Digene (2002) *Annual Report*. Available online at: http://secwatch.com/dige/10k/annual-report/2002/9/30/4393963

Digene (2003) *Annual Report*. Available online at: http://web.archive.org/web/20040723122952/http://www.digene.com/corporate01/Annual_Report/digeneAR03.pdf

Edgerton, D. (2006) *The Shock of the Old: Technology and Global History since 1900*. London: Profile Books.

Fischer, A. H. (2008) 'Practice patterns in HPV testing'. *CAP Today*, August

Gardner, K. (2006) *Early Detection: Women, Cancer and Awareness Campaigns in the Twentieth-century United States*. Chapel Hill: University of North Carolina Press

Gillis, J. (1998) 'Oncor's biotech woes offer a cautionary tale'. *Washington Post*, 9 November

Grebow, M. (2005) 'Digene ads stoke interest in direct-to-consumer marketing'. *IVD Technology*, June

Herbst, A. L., Pickett, K. E., Follen, M. and Noller, K. L. (2001) 'The management of ASCUS cervical cytologic abnormalities and HPV testing: a cautionary note'. *Obstet. Gynecol*. 98(5), pp. 849–851

Hogarth, S., Hopkins, M. and Rodriguez, V. (2012) 'A molecular monopoly? HPV testing, the Pap smear and the molecularisation of cervical cancer screening in the USA'. *Sociology of Health and Illness*, 34(2), pp. 234–50

Hopkins, M., Martin, P., Nightingale, P., Kraft, A. and Mahdi, S. (2007) 'The myth of the biotech revolution: an assessment of technological, clinical and organisational change'. *Research Policy*, 36, 4, pp. 566–589

Hoschar, A. P., Tubbs, R. R. and Hunt, J. L. (2007) 'Clinical testing for low and high risk HPV by ISH in respiratory papillornatosis'. *Laboratory Investigation*, Vol. 87 (March), pp. 223A-223A

Hughes, J. (1997) 'Whigs, prigs, and politics: problems in the historiography of contemporary science' in T. Soderqvest (Ed.) *The Historiography of Science and Technology*. Amsterdam: Harwood, pp.19–37

IARC (1995) *Monographs on the Evaluation of Carcinogenic Risks to Humans: Human Papillomaviruses*, Vol. 64. Lyon: International Agency for Research on Cancer

IARC (2012) *GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012*. Available online at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx

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

Lonky, N., Felix, J. MD, Yathi, M., Naidu, Y. and Wolde-Tsadik, G. (2003) 'Triage of atypical squamous cells of undetermined significance with Hybrid Capture II: colposcopy and histologic human papillomavirus correlation'. *Obstetrics and Gynaecology*, 101(3), pp. 481–489

Lowy, I. (2010) *Preventive Strikes: Women, Pre-cancer and Prophylactic Surgery*. Baltimore: Johns Hopkins University Press

Lowy, I. (2011) *A Woman's Disease: The History of Cervical Cancer*. Oxford: OUP

Luchtefeld, L. (2006) 'Driving awareness'. *MDDI Online*, September. Available online at: www.mddionline.com/article/driving-awareness

Manos, M. M., Wright, D. K., Ting, Y., Broker, T. R. and Wolinsky, S. M. (1989) *US patent no PCT/US1989/003747*. Filed 1989, patent published 1990

Moriarty, A. T., Schwartz, M. R., Eversole, G., Means, M., Clayton, A., Souers, R., Fatheree, L., Tench, W. D., Henry, M. and Wilbur, D. C. (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, pp. 1290–1294

Morioka-Douglas, N. and Hillard, P. (2013) 'No Papanicolaou tests in women younger than 21 years or after hysterectomy for benign disease'. *JAMA Internal Medicine*, online April. doi:10.1001/jamainternmed.2013.316

Moyer, V. A. (U.S. Preventive Services Task Force) (2012) 'Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement'. *Ann Intern Med*., 156: pp. 880–91, W312

Noller, K. L., Bettes, B., Zinberg, S. and Schulkin, J. (2003) 'Cervical cytology screening practices among obstetrician–gynaecologists'. *Obstetrics and Gynaecology* 102(2), pp. 259–265

Oncor (2006) *Annual report, Form 10-K*. Available online at: http://web.archive.org/liveweb/http://www.sec.gov/Archives/edgar/data/806637/0000806637-97-000001.txt

Patient, Consumer, and Public Health Coalition (2015) 'Coalition letter to FDA Commissioner about approving Cobas HPV test alone (without Pap smear)'. Available online at: www.stopcancerfund.org/policy/testimony-briefings/coalition-letter-hpv-test

Perkins, R. B., Anderson, B. L., Gorin, S. S. and Schulkin, J. A. (2013) 'Challenges in cervical cancer prevention: a survey of U.S. obstetrician-gynecologists'. *American Journal of Preventive Medicine* 45(2), pp. 175–181

Poljak, M., Brencic, A., Seme, K., Vince, A. and Marin, I. J. (1999) 'Comparative evaluation of first- and second-generation Digene hybrid capture assays for detection of human papillomaviruses associated with high or intermediate risk for cervical cancer'. *J Clin Microbiol*. Mar; 37(3), pp. 796–7

Ramsey, S. D., Veenstra, D. L., Garrison, L. P. Jr, Carlson, R., Billings, P., Carlson, J. and Sullivan, S. D. (2006) 'Towards evidence-based assessment for coverage and reimbursement of laboratory-based diagnostic and genetic tests'. *American Journal of Managed Care* 12(4), pp. 197–202

Reynolds, L. A. and Tansey, E. M. (Eds) (2009) 'History of cervical cancer and the role of the Human Papillomavirus, 1960–2000'. *Wellcome Trust Witness Seminar Series*, 38

Rosenwald, M. (2005) 'Digene's ads take their case to women'. *Washington Post*, Monday, 21 March

Rotolo, D., Rafols, I., Hopkins, M. and Leydesdorff, L. (2014) 'Scientometric mappings as strategic intelligence for tentative governance of emerging science and technologies'. *SPRU Working Paper Series*, 2014–10, pp. 1–40. Available online at: www.sussex.ac.uk/spru/swps2014-10

Saraiya, M., Berkowitz, Z., Yabroff, K. R., Wideroff, L., Kobrin, S. and Benard, V. (2010) 'Cervical cancer screening with both Human Papillomavirus and Papanicolaou testing *vs* Papanicolaou testing alone: what screening intervals are physicians recommending?' *Arch Intern Med*. 170 (11), pp. 977–986

Saslow, D., Solomon, D., Lawson, H. W., Killackey, M., Kulasingam, S. L., Cain, J., Garcia, F. A., Moriarty, A. T., Waxman, A. G., Wilbur, D. C., Wentzensen, N., Downs, L. S. Jr, Spitzer, M., Moscicki, A. B., Franco, E. L., Stoler, M. H., Schiffman, M., Castle, P. E. and Myers, E. R. (2012) 'American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer'. *Am J ClinPathol* 2012, 137, pp. 516–42

Schiffman, M., Wentzensen, N., Wacholder, S., Kinney, W., Gage, J. and Castle, P. (2011) 'Human papillomavirus testing in the prevention of cervical cancer'. *JNCI*, 103(5), pp. 368–383

Shibata, D., Arnheim, N. and Martin, W. J. (1988) 'Detection of human papilloma virus in paraffin-embedded tissue using the polymerase chain reaction'. *Jnl Exp Med*. 167(1), pp. 225–30

Southwick, K. (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 and Cytochemistry*, 49, 9, pp. 1197–1198

Terry, N., Darragh, T. M. and Waxman, A. G. (2013) 'New ASCCP Guidelines: equal management for equal risk'. *Medscape*. Available online at: www.medscape.com/viewarticle/782362_6 (last accessed 28 May 2013)

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

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

Titus, K. (2006) 'How Pap test automation is playing out'. *CAP Today*, October

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

Walboomers, J. M. M., Jacobs, M. V., Manos, M. M., Bosch, F. X., Kummer, J. A., Shah, K. V., Snijders, P. J. F., Peto, J., Meijer, C. J. L. M. and Muñoz, N. (1999) 'Human papillomavirus is a necessary cause of invasive cervical cancer worldwide'. *J Pathol*. Sep, 189(1), pp. 12–9

Wassermann, S. and Faust, K. (1994) *Social Network Analysis: Methods and Applications*. Cambridge, UK: Cambridge University Press

Wright, T. C. Jr, Cox, J. T., Massad, L. S., Twiggs, L. B. and Wilkinson, E. J. (2002) '2001 consensus guidelines for the management of women with cervical cytological abnormalities'. *JAMA*, 287, 16, pp. 2120–2129

Wright, T. C. Jr, Massad, L. S., Dunton, C. J., Spitzer, M., Wilkinson, E. J. and Solomon, D. (2007) '2006 Consensus guidelines for the management of women with abnormal cervical cancer screening tests'. *American Journal of Obstetrics & Gynaecology*, October, pp. 346–355

Yuxiang, G., Jay, G., Khorshidi Hossein, S., Mishra Nrusingha, C. and Szweda, P. for Oncor Inc. (1996) *Modified nucleotides for nucleic acid labelling*. Patent Number WO 1996041006 A1 (APPLICANT NAME: ONCOR INC)

zur Hausen, H. (1987) 'Papillomaviruses in human cancer'. *Applied Pathology*, 5, pp. 19–24

zur Hausen, H. (2006) 'Perspectives of contemporary papillomavirus research'. *Vaccine* 24S3 (2006), pp. S3/iii–S3/iv