From Papanicolaou to Papilloma: the corporatisation of cancer screening innovation

Stuart Hogarth, King’s College London
How did a small molecular diagnostics start-up come to dominate the market for DNA-based cervical cancer screening in the USA?
The promise of molecularisation

We expect gene-based diagnostic tests will create a fundamental shift in both the practice of medicine and the economics of the diagnostics industry.

Digene 2002 Annual Report
The pharmaceuticalisation of the diagnostics industry

The translation of pharmaceutical business practices and business models to the IVD industry
“Early detection emerging as a new opportunity
A wave of new IVD-based tests has started to reach the market and could offer new hope for early detection of major cancers...
If this model were validated, drug-like blockbuster revenues could follow for some tests. The commercial payback for one such test could surpass the revenues of a companion diagnostic by a multiple of 10.”

PriceWaterhouseCoopers, 2011
The early opportunity

**US National Cancer Institute**

“The Early Detection Research Network (EDRN) ... brings together dozens of institutions to help accelerate the translation of biomarker information into clinical applications and to evaluate new ways of testing cancer in its earliest stages and for cancer risk.”
The early opportunity

The Canary Center at Stanford for Cancer Early Detection is the only facility in the world that integrates both blood and imaging-based diagnostic research in cancer early detection.
Cervical cancer screening

The pap paradox

• National programmes for screening women for cervical cancer exist in most developed countries
• A success story - widely credited with lowering cervical cancer mortality internationally – “the most effective screening test for cancer that has ever been devised”

BUT

• Subjective, error prone and expensive
• False negative rates of 15-50%
• In USA 9% of tests are too ambiguous to be classed as positive or negative (ASCUS)
Cervical cancer screening

Commercial promise

• Limitations of Pap smear test provide opportunity
• Companies estimate potential value of US market between **$500 million and $1 billion**
• There are over 100 subtypes of HPV. Most are harmless. But persistence of certain HPV types can cause cell changes which can lead to cervical cancer.
• Cornell University, 1917 uses vaginal smears for research on reproductive cycle
• 1928 paper on exfoliated cancer cells in women’s vaginal smears – poorly received
• 1939 – Papanicolaou returns to working on pap smear as cancer detection tool
• 1941 – Papanicolaou publishes new paper and receives funding from Commonwealth Fund
• 1945 – American Cancer Society sponsors first National Cytology Conference, National Cancer Institute also funds research on pap smear
Professionalisation

• 1947 – Papanicolaou begins to offer training courses in cytology
• Pap smear gains support of
  • American Society of Clinical Pathologists
  • College of American Pathologists,
  • International Union Against Cancer
• The emergence of cervical cytology
• Inter-Society Cytology Council established
Industry steps in

- The emergence of automation
- Liquid-based cytology

SPECIMEN collection
Established business model: patents on platforms
Digene’s vision

We expect gene-based diagnostic tests will create a fundamental shift in both the practice of medicine and the economics of the diagnostics industry.

Digene 2002 Annual Report
Commercial promise

... companies that develop gene-based diagnostic tests may obtain intellectual property protection and, therefore, may generate higher margins.

Digene 2002 Annual Report
A viral model of cancer

- 1983 - discovery of tumorigenic virus type HPV 16/18 by Harald zur Hausen
- 1984 (?) - Atilla Lorincz joins BRL-Life Technologies, enters collaboration with Georgetown University to develop HPV test leading to discovery (and patenting) of new HPV types
Finding the right job for the tool

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 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.

Former Digene executive, interview 2010
Three possible roles for HPV testing in cervical cancer screening

<table>
<thead>
<tr>
<th>Testing protocol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-US triage (reflex)</td>
<td>Pap remains initial screening test, HPV is used as a reflex follow-up, reducing need for colposcopy</td>
</tr>
<tr>
<td>Adjunctive screen with pap</td>
<td>Pap and HPV used as joint primary screen allowing less frequent screening for women who test negative for both tests.</td>
</tr>
<tr>
<td>Sole primary screening test</td>
<td>HPV used as initial screening test, Pap may be used to follow-up HPV-positive women.</td>
</tr>
</tbody>
</table>
1988: first HPV test with FDA approval

**ViraPap®—
the diagnostic adjunct
to the Pap smear**

The value of the Pap smear in reducing mortality from cervical cancer is well-recognized. However, it has been estimated that in patients with known cervical lesions, approximately 30% of Pap smears may be interpreted as normal.

In a study of 2,186 patients to determine the utility of HPV testing as an ancillary test to the Pap smear, 359 slides were reread, giving the following results:

<table>
<thead>
<tr>
<th>Cytology</th>
<th>HPV</th>
<th>Pap Smear Reread Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>−</td>
<td>+</td>
<td>17.5% of Pap smears from women with HPV infection were reclassified as abnormal upon reread.</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>2.6% of Pap smears in this control group of women without detectable HPV were reclassified as abnormal upon reread.</td>
</tr>
</tbody>
</table>

BRL-Life Technologies trade advert for ViraPap test, date unknown (post-FDA approval)
Resistance is fatal

... the cytologists when they got whiff of the fact that ... we were thinking of replacing the pap smear - they basically fought back in a very negative way ... 

Former Digene executive, interview 2010
Utility of ViraPap Remains To Be Established

ViraPap, a test to screen women for human papillomavirus (the agent that causes genital warts), can improve the accuracy of a Pap smear result, according to the test’s developers.

But, while some doctors advocate use of the test, others question its necessity. Reluctance by the medical community to embrace this high-tech, costly ($43 to $72) test with as-yet-unproven relevance has stymied its widespread use. Those familiar with the field agree, however, that long-term studies will determine the test’s utility.

Lorincz acknowledges that use of ViraPap is still controversial, but data from long-term, prospective studies could change the situation. “If we could tell women, ‘you’ve got HPV-16, and our studies show that over a period of 5 years, you’ve got a 20% chance of developing a cervical lesion’—that would be something concrete,” said Lorincz.

Journal of National Cancer Institute, February 1990
A new phase in development

- 1990 – Digene acquire Life Technologies’ diagnostics division
  - Lorincz (and HPV IP) move to Digene
  - Digene develop new strategy informed by failure of ViraPap
Digene’s strategy
Lockdown HPV patents

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

Owners of patents on HPV types and other intellectual property used over three generations of HPV testing kits
Defending the monopoly

HPV patent litigation with rivals in United States

• 2001 - Digene sues Ventana (and subsequently Beckman Coulter)
• 2002 - Enzo Biochem sues Digene
• 2004 - Georgetown University sues Digene
• 2005 - Third Wave sues Digene
• 2006 - Digene files against Roche (Gen-Probe joint the suit)
• 2007 - Digene sues Third Wave
Build a proprietary platform

1992
Digene patent new technology platform – Hybrid Capture
## Demonstrate utility

**HPV clinical trials in which Digene participated in late 1990s**

<table>
<thead>
<tr>
<th>Country</th>
<th>Lead Investigator</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>National Cancer Institute (ALTS Trial)</td>
<td>7,000</td>
</tr>
<tr>
<td>Canada</td>
<td>Newfoundland Department of Health</td>
<td>3,000</td>
</tr>
<tr>
<td>Mexico</td>
<td>Johns Hopkin; Mexican Government</td>
<td>7,500</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Free University of Amsterdam</td>
<td>40,000</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Imperial Cancer Research Fund</td>
<td>10,000</td>
</tr>
<tr>
<td>Germany</td>
<td>University of Tubingen</td>
<td>8,000</td>
</tr>
<tr>
<td>Russia</td>
<td>University of Turku, Finland</td>
<td>12,000</td>
</tr>
<tr>
<td>Brazil</td>
<td>University of Rio Grande do Sul</td>
<td>2,000</td>
</tr>
<tr>
<td>Argentina</td>
<td>Institut Papincolau</td>
<td>1,000</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>National Cancer Institute</td>
<td>10,000</td>
</tr>
<tr>
<td>China</td>
<td>Cleveland Clinic Foundation</td>
<td>2,500</td>
</tr>
</tbody>
</table>

*Source: Digene Annual Report 1999*
A monopoly on evidence

“The Hybrid Capture assay is the de facto standard because Digene made it available for research early on and got a huge amount of data, which allows good clinical correlation. It’s now difficult for any other test to achieve that.”

Elizabeth R. Unger, acting chief of the Chronic Viral Diseases Branch, Centers for Disease Control and Prevention. Quoted in CAP Today, 2010
A monopoly on evidence

Top 10 public/private organisations in HPV diagnostics up to 2011

<table>
<thead>
<tr>
<th>Public Organization</th>
<th>Number of Publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. NCI</td>
<td>278</td>
</tr>
<tr>
<td>2. JOHNS HOPKINS UNIV</td>
<td>213</td>
</tr>
<tr>
<td>3. INT AGCY RES CANC</td>
<td>149</td>
</tr>
<tr>
<td>4. UNIV WASHINGTON</td>
<td>121</td>
</tr>
<tr>
<td>5. HARVARD UNIV</td>
<td>114</td>
</tr>
<tr>
<td>6. MCGILL UNIV</td>
<td>93</td>
</tr>
<tr>
<td>7. UNIV CALIF SAN FRANCISCO</td>
<td>92</td>
</tr>
<tr>
<td>8. ALBERT EINSTEIN COLL MED</td>
<td>84</td>
</tr>
<tr>
<td>9. CTR DIS CONTROL &amp; PREVENT</td>
<td>81</td>
</tr>
<tr>
<td>10. UNIV TEXAS</td>
<td>80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Private Organization</th>
<th>Number of Publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. DIGENE CORP.</td>
<td>78</td>
</tr>
<tr>
<td>2. DDL DIAGNOSTIC LABORATORY</td>
<td>63</td>
</tr>
<tr>
<td>3. MERCK &amp; CO. INC.</td>
<td>60</td>
</tr>
<tr>
<td>4. GLAXOSMITHKLINE BIOLOGICALS</td>
<td>50</td>
</tr>
<tr>
<td>5. ROCHE MOLECULAR DIAGNOSTIC</td>
<td>30</td>
</tr>
<tr>
<td>6. INFORMATION MNGT SERVICE</td>
<td>30</td>
</tr>
<tr>
<td>7. ABBOTT MOLECULAR INC.</td>
<td>15</td>
</tr>
<tr>
<td>8. NORCHIP A.S.</td>
<td>10</td>
</tr>
<tr>
<td>9. CYTYC CORP.</td>
<td>9</td>
</tr>
<tr>
<td>10. CETUS CORP.</td>
<td>8</td>
</tr>
</tbody>
</table>
A new model for biomarker R&D?

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

Digene execs, *IVD Technology*, July 2006
Enrol support
1999
FDA approve Digene’s HC2 test for ASCUS triage
... some people were very critical of ALTS because they said well here’s a company you know involved in FDA, an NIH trial, but you know from my standpoint it was very clear, the outcome was very clear, right? There was only one FDA approved test, we weren’t going to use any other technology that wasn't FDA approved ... and it was very clear from a standpoint of HPV testing, ALTS was either going to prove HPV testing worked, or Digene was going to go away and there would be no HPV testing.

Cytopathologist, 2013
... the two products that actually I think made it to the market big time, which was Oncotype Dx ... and HPV. I think what they had in common was ... actually the fact that those groups had credibility that vibrated beyond the study, that when you have thought leaders who are at the forefront of NIH diagnostic development, it’s disingenuous to say that doesn’t have an impact on the perception within the community, or the perception within the government... So it doesn’t hurt to have NIH thought leaders bankrolling you and then helping you design your studies, helping you analyse your studies and then going out and saying nice things about your assay, that’s not harmful.

Ex-FDA official, 2013
Professional endorsement

- 2001 – American Society for Colposcopy and Cervical Pathology (ASCCP) Consensus Guidelines support use of HC2 test for ASCUS triage

“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.”

Interview with USA laboratory director, 2009
The role of Key Opinion Leaders

- 2001 – American Society for Colposcopy and Cervical Pathology (ASCCP) Consensus Guidelines support use of HC2 test for ASCUS triage

- 41 members of the ASCCP working groups
- 7 individuals disclosed links with Digene (research grants, honoraria and consultancy work)
- 7 members in the working group which developed the ASCUS management recommendations
- four of the seven participants had collaborated with Digene, three of them on the ALTS trial
- the fourth was Tom Wright, the lead author of the guidelines, whose financial disclosure statement revealed that he had received research funding from Digene, consulted for the firm and been on their speakers bureau.
The role of Key Opinion Leaders

‘[The] bar has been raised for bringing forward newer HPV diagnostics ... Any new test must document its performance relative to this [HC2] standard’

Mark Stoler, editorial accompanying ASCCP guidelines
The role of Key Opinion Leaders

Attacks on credibility of rival tests by Digene and scientific collaborators

"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."

Mark Schiffman, NCI
2005 CAP Today
The role of Key Opinion Leaders

- 2009 FDA approve Third Wave/Hologic Cervista test
- 2010 - Kinney, Stoler and Castle publish criticism of the test:
  “A recent US Food and Drug Administration (FDA)-approved HPV test, Cervista (Hologic, Bedford, MA), demonstrated excessive test positivity -2 to 4 times more positive than the other FDA-approved HPV test-from its premarketing approval trial. The poor specificity of Cervista raises questions about the safety and applicability of using this test in routine cervical cancer screening.”

American Journal of Clinical Pathology, Aug;134(2):193-9
“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”

ASCUS triage – HPV’s low hanging fruit
"Our goal is to replace the Pap smear."
Evan Jones, Digene CEO/chairman

"The Pap smear has a long tradition of reducing cervical cancer... We don't want to dislodge good cervical cancer screening unnecessarily."
Mark Schiffman, (ALTS Principal Investigator), National Cancer Institute

Washington Post, 31 January 2001
Moving centre stage

- 2002/3 - new guidelines from American Cancer Society and American College of Obstetricians and Gynaecologists cite ASCCP on ASCUS triage and support use as adjunct screen in women 30+ years
- 2003 – FDA approve adjunct screening use, HC2 rebranded as DNAwithPap
Advertising and advocacy: a new marketing strategy

Yes, so the thing that was different about Digene was we took almost a pharma approach to the marketing of a diagnostic.

Former Digene employee, interview 2013
The doctor’s not expecting you
Partner with women’s advocacy groups

Each year, thousands of women in our country die needlessly from cervical cancer – a highly preventable disease. Medical experts now know what causes cervical cancer and new and emerging technologies, such as HPV testing and eventual vaccines, give our country a real opportunity to make it the first major women’s cancer we can eliminate.

Women In Government believes we must all seize this opportunity. Thus, we have made eliminating cervical cancer over the next 10 years one of our organization’s top priorities. In 2004, we created our Challenge to Eliminate Cervical Cancer Campaign, which engages state legislators in passing legislation and resolutions that improve cervical cancer prevention efforts in their states. Our objective is to ensure that all women have access to cervical cancer education and effective screening programs that utilize the most advanced technologies available.

A Call to Action: the ‘State’ of Cervical Cancer Prevention in America, Women in Government, 2005
The customer is always right

If you’re a gambling woman, then getting just a Pap test is fine.

Almost all cervical cancers are caused by a virus – the human papillomavirus (HPV). A Pap test looks for the abnormal cells caused by HPV but may not find them until it’s too late. Only the HPV test can directly detect the virus and is nearly 100% accurate.

When used along with a Pap, the HPV test can help your doctor reduce your chances of developing cervical cancer and is approved for screening women 30 and over.

Learn more before your next doctor’s appointment.

www.thenhpctest.com 877-HPV-FACT

Digene print advert straplines, 2005

You’re not failing your Pap test but it might be failing you.

Almost all cervical cancers are caused by a virus – the human papillomavirus (HPV). A Pap test looks for the abnormal cells caused by HPV but may not find them until it’s too late. Only the HPV test can directly detect the virus and is nearly 100% accurate.

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Going for growth

Rapid growth across key metro markets - through Summer 2006

<table>
<thead>
<tr>
<th>Metro Market</th>
<th>Total high-decile market (SM)*</th>
<th>Penetration in Key Metro Markets</th>
<th>% Increase in Penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>New York</td>
<td>$40</td>
<td>84%</td>
<td>84%</td>
</tr>
<tr>
<td>Chicago</td>
<td>$20</td>
<td>58%</td>
<td>58%</td>
</tr>
<tr>
<td>Philadelphia</td>
<td>$20</td>
<td>111%</td>
<td>111%</td>
</tr>
<tr>
<td>Baltimore</td>
<td>$15</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>Dallas</td>
<td>$15</td>
<td>67%</td>
<td>67%</td>
</tr>
<tr>
<td>Washington, DC</td>
<td>$10</td>
<td>36%</td>
<td>36%</td>
</tr>
<tr>
<td>Boston</td>
<td>$10</td>
<td>67%</td>
<td>67%</td>
</tr>
<tr>
<td>San Francisco</td>
<td>$10</td>
<td>18%</td>
<td>18%</td>
</tr>
<tr>
<td>Houston</td>
<td>$10</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>Miami</td>
<td>$10</td>
<td>36%</td>
<td>36%</td>
</tr>
</tbody>
</table>

*Digene estimates

Source: Dgene presentation, 2006
A growing market

- 2007 - Qiagen acquire Digene for $1.3 billion
- Market continues to grow, including entry of competitors
  - 2009 - Third Wave (now Hologic)
  - 2011 - Gen-Probe (now Hologic)
  - 2011 - Roche Molecular
- 2012 - USPSTF guidance and new guidance from ACS
- 2013 - Roche submit PMA for HPV primary screening based on ATHENA trial
Back to normal?

• Competition is increasingly about the quality of the platform
  • comparable analytic/clinical performance
  • Key advantage will be in quality of automation
  • Competition driving price down
  • Back to high-volume, low profit-margin

BUT

• Competition also on quality and size of clinical evidence base (Roche ATHENA trial)
How much longer is he going to be?
The power of Pap
The power of the network
The power of the entrenched actors

American Cancer Society

Hybrid Capture

ASCCP
Some questions

• Does pharmaceuticalisation work outside the USA?
  • Slow uptake of HPV tests (take-off as patents expire)
  • Huge number of rival tests on EU market (no IP wars)
  • Rejection of industry pressure (e.g. UK)

BUT

• Shift to HPV primary screening may be faster and broader
Conclusions

- Diagnostics companies are drivers of medicalisation
- Public policy implications
  - What constitutes responsible diagnostic innovation?
  - How should public funding support proprietary tests?
  - How much are we willing to pay for novel diagnostics?

BUT

- Pharmaceuticalisation of IVD industry is partial/contingent and still affects only small part of diagnostics sector
- Most companies remain wedded to platform IP and very limited investment in biomarker validation
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Thanks for listening

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genevalues
A blog about the ethics and economics of personalised medicine