


Challenges of Bringing Novel Diagnostics to Market

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Realistic Expectations; *how to add a test into existing market*



- \$40 Billion Market
- 80% market supported and supplied by 4/5 large companies
- 40% market in the US
- High level of equipment reliance
 - Extremely challenging for smaller entities to go it alone
- High R&D Costs & short product lifecycles major challenge
- High Level of Corporate Consolidation

Assessing Opportunities and value in Diagnostic Markets




- Purpose of test
 - Diagnostic
 - Value dependent on Disease and prevalence
 - Screening
 - Value dependent on burden and relevance, CaCx, Breast, prostate
 - Management
 - Value based on incidence and treatment availability
- Niches (high growth areas)
 - Point of care
 - Molecular & Genetics
- Market Types
 - Europe vs Japan vs US
 - Must succeed in US market to maximise IVD value
 - Low Resource markets vs First world
 - National health systems (reimbursements) vs free market (Patient pays)

Market needs Product must fulfill a Need



- Life Threatening
 - Cardiovascular
 - Cancer/Malignancies
 - Infectious Diseases
- Quality of Life
 - Genetics
 - Monitoring, Diabetics HbA1c

Product Launch must equate to Commercial success



- Diagnostics are now a crucial and complimentary component to the pharma industry maximising the utility of Novel agents/treatments by diagnosing, identifying risk and the management of targeted diseases
- Historically, diagnostics have been seen as a quicker and easier commercialisation process than Pharma, this has changed somewhat with the advent of more complex diagnostic systems and higher costs to bring products to market

Ideal New Diagnostic (Novel or Not)



- Quicker}
- Simpler} *Compared to existing technology/methodology*
- Cheaper}
- Unique (new target)
- Single target/entity
- Meets a health market need and value
 - Reduction in death
 - Reduction in disease burden
 - Reduction in disease management cost

Novel Products can be:



- Supportive to current management/detection
 - Improvement based
- Disruptive (displace existing infrastructure and interests)
- Revolutionary, change the paradigm
- Opportunistic; Emerging public health priorities
 - Flu/SARS
 - BioTerrorism

Novel Products



- Platform and enabling technology
 - PCR
 - Multiplexing
 - Use of mass Spectrometry
- Product/Agent
 - BNP
 - HCV
 - HPV
 - MicroArray- CGH genetics and pre disposition

Issues to Consider with new Targets



- Multiple Targets
 - Difficult to validate together
 - Complex regulatory process
- Platform technology may be restricted
 - Limits licensing direction
 - Forces commercialisation onto a less than optimal technology platform

Options for Commercialisation



- Licensing IP with Royalty stream
- Establish Company and Develop product
 - Costly
- Requires a great deal of expertise
 - Merge or be acquired

Diagnostic Business does not maintain many single product companies; for too long at least

Road to Commercial Success



- Discovery
- Proof of Principle
- External pre-Validation
- Securing IP
- Licensing or "go alone strategy"
- Product Development
- Clinical Validation
- Regulatory Approval
- Market recognition (incorporation into guidelines, Standard of Care)
- Reimbursement (or private market acceptance)
- Marketing to alter conditions/attitudes
- \$\$\$\$ of costs for sales and support
- Profitability/Value

Regulatory Hurdles



- GMP Compliance
- World wide Regulatory harmonisation
 - CE Marking
- FDA
 - 510k Equivalency (90 days)
 - PMA Pre Market Approval, Clinical Use Claim (2-3 years)
 - CBER, Biological (2- 3 years)

PMA; and you wait



- Premarket approval by FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices.
- Class III device as one that supports or sustains human life or is of substantial importance in preventing impairment of human health or presents a potential, unreasonable risk of illness or injury. All devices placed into Class III are subject to premarket approval requirements.

Reimbursement Hurdles



- Australia/UK
 - MSAC
 - Cost effectiveness and efficiency
 - Limited new tests included onto Medicare since 2000
 - limited use of HPV (after 3 applications)
 - BNP
 - HCV and HBV viral load
 - Fragile X
 - BCR-ABL for CML monitoring
 - Tests for CML diagnosis
 - Thrombophilia
 - FOBT
 - NICE
- USA
 - HMO's
 - Medicaid/Medicare
- Japan
 - Complex, Slow, Expensive

Current IVD Assessments in front of MSAC



In Assessment stage

[1122 - Automated Liquid Based Cytology](#)

[1125 - Molecular Testing for the Diagnosis of Myeloproliferative Disorders](#)

[1126 - Molecular Testing for Developmental Delay/Mental Retardation](#)

[1127 - Genotypic Resistance Testing of Antiretrovirals in HIV](#)

Completed awaiting publication

[Ref 35 c - PET for lymphoma](#)

[Ref 38 - Gene amplification tests for determining HER-2 status in Breast Cancer](#)

[Ref 39 - Human papilloma virus – triage for PAP smears](#)

IVD's that have Failed

INR POC Testing for monitoring patients receiving warfarin

Urea breath tests for H.pylori

UroVysion FISH test for Bladder Cancer

Liquid Based Cytology

Fetal Fibronectin test for preterm labour

CLO-Test

Issues for Genetic Arrays



- Regulatory Complexities
 - What do you do with the extra information
- Relevance and Analysis
 - Validation challenges, statistical weight
- Cost
- Will it attract suitable reimbursement
 - No

Time to market



- Always significantly longer than planned or expected,
- More complex or novel, the longer it takes
- Risk correlates to reward
- 5-10 years
 - Product Validation
 - Product registration
 - Guidelines and acceptance
- More difficult for others to follow;

Examples



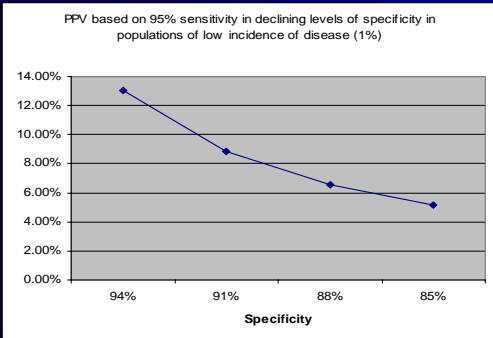
Effect of varying sensitivities and specificities in clinical performance on population of 10,000 with incidence of CIN2/3 of 1%

High Specificity	Sensitivity	Specificity	true positives detected	false positives detected	PPV	NPV
	98%	94%	98	632	13.43%	99.98%
	95%	94%	95	632	13.07%	99.95%
	90%	94%	90	632	12.47%	99.89%
	85%	94%	85	632	11.86%	99.84%
	80%	94%	80	632	11.24%	99.78%

Medium Specificity	Sensitivity	Specificity	true positives detected	false positives	PPV	NPV
	98%	91%	98	979	9.10%	99.98%
	95%	91%	95	979	8.84%	99.94%
	90%	91%	90	979	8.42%	99.89%
	85%	91%	85	979	7.99%	99.83%
	80%	91%	80	979	7.55%	99.78%

Low Specificity	Sensitivity	Specificity	true positives detected	false positives	PPV	NPV
	98%	85%	98	1747	5.31%	99.98%
	95%	85%	95	1747	5.18%	99.94%
	90%	85%	90	1747	4.90%	99.88%
	85%	85%	85	1747	4.64%	99.82%
	80%	85%	80	1747	4.38%	99.76%

Effects on Positive Predictive Values with declining Specificities (low incidence)



Would such a test succeed as a screening test

- Low predictive value
 - Lots of false positives
- High follow up costs for triage and confirmation
- Overall, process is Costly
- Not effective or efficient

Cervical Cancer-background

- 2nd leading cancer death among women world wide
- Generally a young women's disease
- 100% preventable
- Complex but cheap and successful screening test in place
- Need to perform test frequently
- Vaccine now available

PREDICTED NUMBER OF CERVICAL CANCER CASES IN 2020 BY WORLD AREA AND AGE

PROJECTIONS ASSUME RATES ESTIMATED FOR 2002 HOLD INTO THE FUTURE

	2002	2020 (% change)	2020 (% burden)
WORLD	493,000	702,500 (42%)	100%
Women aged <65	396,500	549,000 (38%)	78%
Women aged ≥65	96,500	153,500 (59%)	22%
LESS DEVEL. AREAS	409,000	639,500 (56%)	83%
Women aged <65	336,000	507,500 (51%)	79%
Women aged ≥65	73,000	132,000 (80%)	21%
MORE DEVEL. AREAS	83,000	92,500 (11%)	17%
Women aged <65	60,000	62,500 (03%)	67%
Women aged ≥65	23,000	30,000 (31%)	33%

GLOBOCAN 2002

Stakeholders in Cervical cancer Screening

- Laboratories
 - Virus/Molecular vs Cytology
- Governments
 - Policy
 - Costs of change
- Physicians
 - General practitioners
 - Gynaecologists and Colposcopists
 - Gynaecological Oncologists
- Vaccine manufacturers
- Women

JOURNAL OF PATHOLOGY
J. Pathol. 189: 12-19 (1999)

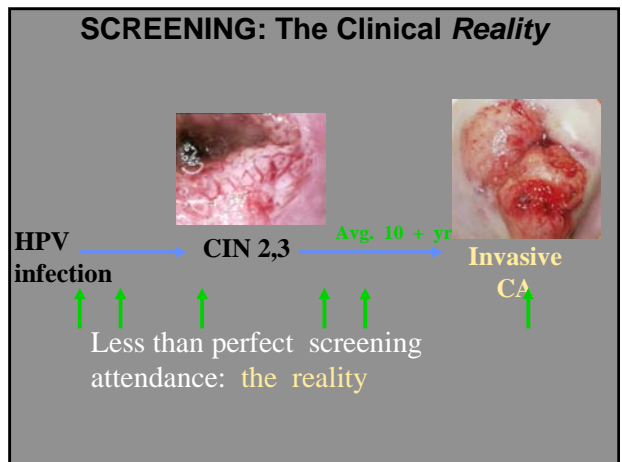
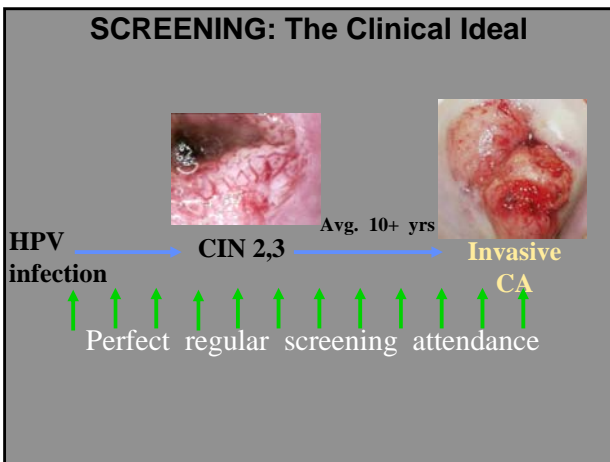
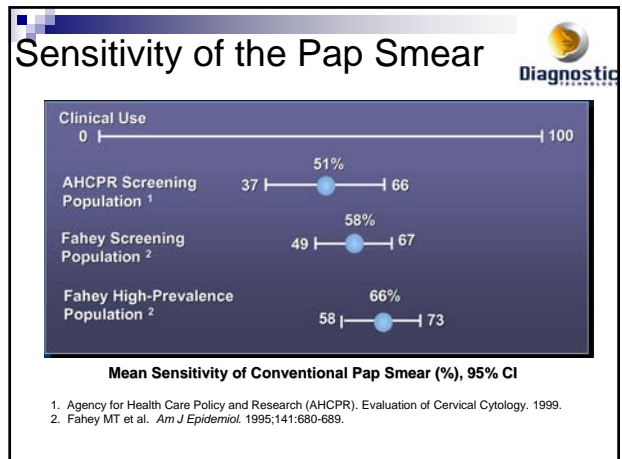
HUMAN PAPILLOMAVIRUS IS A NECESSARY CAUSE OF INVASIVE CERVICAL CANCER WORLDWIDE

JAN M. M. WALBOOMERS¹*, MARCEL V. JACOBS¹, M. MICHELE MANOS², F. XAVIER BOSCH³, J. ALAIN KUMMER¹, KEERTI V. SHAH⁴, PETER J. F. SNIDERS⁵, JULIAN PETO⁶, CHRIS J. L. M. MEIJER¹ AND NUBIA MUÑOZ²

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SUMMARY

A recent report that 93 per cent of invasive cervical cancers worldwide contain human papillomavirus (HPV) may be an underestimate, due to sample inadequacy or integration events affecting the HPV L1 gene, which is the target of the polymerase chain reaction (PCR)-based test which was used. The formerly HPV-negative cases from this study have therefore been reanalysed for HPV serum antibodies and HPV DNA. Serology for HPV 16 VLPs, E6, and E7 antibodies was performed on 49 of the 66 cases which were HPV-negative and a sample of 48 of the 866 cases which were HPV-positive in the original study. Moreover, 55 of the 66 formerly HPV-negative biopsies were also reanalysed by a sandwich procedure in which the outer sections in a series of sections are used for histological review, while the inner sections are assayed by three different HPV PCR assays targeting different open reading frames (ORFs). No significant difference was found in serology for HPV 16 proteins between the cases that were originally HPV PCR-negative and -positive. Type-specific E7 PCR for 14 high-risk HPV types detected HPV DNA in 38 (69 per cent) of the 55 originally HPV-negative and amplifiable specimens. The HPV types detected were 16, 18, 31, 33, 39, 45, 52, and 58. Two (4 per cent) additional cases were only HPV DNA-positive by E1 and/or L1 consensus PCR. Histological analysis of the 55 specimens revealed that 21 were qualitatively inadequate. Only two of the 34 adequate samples were HPV-negative on all PCR tests, as against 13 of the 21 that were inadequate ($p < 0.001$). Combining the data from this and the previous study and excluding inadequate specimens, the worldwide HPV prevalence in cervical carcinomas is 99.7 per cent. The presence of HPV in virtually all cervical cancers implies the highest worldwide attributable fraction so far reported for a specific cause of any major human cancer. The extreme rarity of HPV-negative cancers reinforces the rationale for HPV testing in addition to, or even instead of, cervical cytology in routine cervical screening. Copyright © 1999 John Wiley & Sons, Ltd.




“The best strategy for preventing cervical cancer is to use the most accurate test at the longest possible interval.”

Dr. Jack Cuzick
American Cancer Society Guideline Group
April 9, 2002

If All Cervical Cancer is Caused by HPV;

Why then hasn't it been used as a screening test?

- Not all HPV causes Cervical Cancer; In fact it rarely causes Cervical Cancer, HPV infection does not equate to disease
- Its not a single virus
- Cytology has/is working, infrastructure in place



The problems to overcome

- Interests in existing technology
 - Pap smears
 - Pathology Labs
 - Doctor visits
 - New Liquid Based Cytology tests
 - Colposcopists
- Perceptions of higher costs
- Use of STI test for cancer screening
- Frequency of infection amongst the population

Int. J. Cancer, 119, 000-000 (2006)
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Overview of the European and North American studies on HPV testing in primary cervical cancer screening

Jack Cuzick^{1*}, Christine Clavel², Karl-Ulrich Petry³, Chris J.L.M. Meijer⁴, Heike Hoyer⁵, Samuel Ratnam⁶, Anne Starewicz⁷, Philippe Birembaut⁸, Shadi Kulkarni⁹, Peter Sankari¹⁰ and Thomas Hüne¹¹

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HPV DNA test for high risk types have proven higher sensitivity to detect pre-cancers CIN 2+

Cuzick et al IJC April 2006

> 60,000 women from UK, Fr, Ger, NL, USA and Canada
 HPV test shows consistently higher sensitivity

	Clinical Sensitivity	Clinical Specificity
Cytology	53.0%	96.3%
HPV (most hc2)	96.1%	90.7%

HC2 HPV Clinical Validation

Author	Year	No. of Women
Lorincz	92	2,627
Cuzick	99	1,703
Bozzetti	00	977
Ratnam	00	2,098
Schiffman	00	8,554
Wright	00	1,365
Zielinski	01	278
Solomon	01	3,488
Bellinson	01	1,397
Clavel	01	5,671
Pretorius	02	845


Author	Year	No. of Women
Kulasingam	02	4,075
Salmeron	03	7,732
Sherman	03	20,810
Petry	03	7,592
Kulmala	04	1,511
Castle	05	5,060 (ALTS 20k+)
Schiffman	05	10,000
Schiffman	05	3,363
Soderlund	05	239
Fetterman	05	123,909
Roneo	06	16,706

215,000+ women, histological end points
 Hundreds of thousands of samples

True Clinical Validation

Established Clinical Uses based on clinical studies using Digene HPV DNA test

- Management of women with ASCUS
- Post-treatment follow-up for CIN 2,3
- HPV Adjunctive (US) and Primary screening




Evolution of the Hybrid Capture 2 & HPV DNA Testing

- 1998 KAISER and NCI Studies
- 2000 FDA approves hc2 High-Risk HPV Test for ASCUS Management
- 2001 NCI ALTS Study Published
- 2001 ASCCP Consensus Guidelines
- 2002 American Cancer Society Guidelines
- 2003 FDA approves HC2 for Primary Adjunctive Screening
- 2003 ACOG Practice Bulletin
- 2004 Patient Management Guidelines Published
- 2004 IARC WHO Recommendations
- 2007 ACCP Guideline/Position Statement

Guidelines/reimbursement exist

- Germany, Austria, France, Italy, Belgium, Spain, Norway, European Union, Australia, Korea, China, Mexico, Brazil, USA

Sample & Assay Technologies



Resistance in the face of Evidence

- Pap Smears only proven method
 - Drives the Pathology test menu
 - Differentiates the quality of the lab
- HPV positivity will make the patients too anxious
- Too many women would be positive
- HPV has not yet been proven
- It will cost too much

Creating a mood and need for Change



- Medical Press
- Women's magazines
- General Press
- Political Lobbying
- CME programs
- TV advertising

POSSIBLE ALGORITHM FOR THE USE OF HPV TESTING AS THE SOLE PRIMARY SCREENING MODALITY FOR WOMEN AGES 25-64, FOLLOWED BY PAP TRIAGE OF HPV POSITIVE WOMEN

