

Figures relating to potential impact

Current HPV testing market worldwide	
Sales 2012	350 Mio. EUR
Growth rate:	6%

Table 1: Worldwide HPV-related diagnostic market

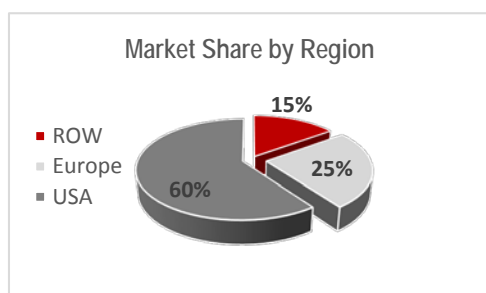


Figure 1: Market Share by Region

Test/Method	Reimbursement Number	Reimbursement in €	Description
HPV-DNA	EBM 32820, EBM 32859	34.40	only after CIN I – CIN III
HPV-DNA	private (GOÄ)(4780+4783+4785)	113.96	-
Cytology (PAP-smear)	EBM 01733	7.50	for early cancer diagnosis
Cytology (PAP-smear)	private (GOÄ) 4851+ 298	10.20	for early cancer diagnosis

Table 2: HPV reimbursement in Germany

Test name	Test system/method	Price/test in €	Weakness of previous test systems	PIPAWELL E7 test strengths
PIPAWELL E7	HPV protein based ELISA	10-15	n.a.	n.a.
ThinPrep Test (Hologic) liquid based cytology (Cytic) PAPNET (Neuromedical Systems) AUTOPAD (Neopath Inc.)	Regular PapSmear (no HPV detection)	10-60	General low sensitivities (55%) High risk of false-positive	Objective, highly cost efficient and precise test result due to molecular markers
AID GenID HPV, Roche (Amlisor, Cobas 4800, Linear Array), Quiagen (careHPV, eHC,HC2),	HPV DNA test	40-100	No discrimination between transient and persistent infection, detecting (hr, lr-) HPV	Specific detection of persistent infection;

Hologic (Cervista), BioRad (HR-HPV Dx PCR), Innogenetics (InnoLiPA), Greiner (Papillocheck), Abbott (RT HPV)			DNA in a patient is of no clinical value in predicting the regression or progression patterns of disease (CIN lesions) caused by HPV.	test identifies viral oncoprotein which drive cervical carcinogenesis; the E7 ELISA test allows for subsequent prediction of cancer.
Aptima (GenProbe), OncoTest (InCellDx), PreTect Proofer (Norchip)	HPV mRNA test	100-150	No discrimination between transient and persistent infection	Specific detection of persistent infection
Multiplex HPV Genotyping Kit (Multimetrix)	HPV genotyping	280	Indirect marker of progression, based on the epidemiologically defined "malignant potential" of each high-risk type	Direct and specific progression marker, based on the increased expression of E7 oncoprotein
E6 protein, strip assay (Arbor Vitae),	HPV protein	60	Strip assay; low sensitivity; two hrHPV types only	High sensitivity; available for up to 12 hrHPV types
CINtec plus (mtm Roche), ProExC (Becton Dickinson)	Cellular proteins	28	Dependence on costly and time consuming immuno- cytology technique and surrogate markers	independent of cytology, ELISA-based robust technology

Table 3: Human papillomavirus (HPV) based tests offered by competitors

The MIKROGEN HPV E7 test reduces the need to perform uncomfortable colposcopies

The current State of HPV testing involves major deficits with negative effects on patients through high rates of unneeded follow-up examination

Currently HPV-testing is mostly performed by a combination of a Pap-test and a HPV-DNA test

- Pap-test: Detection of abnormal cells
- HPV-DNA test: Detection of viral nucleic acids
- These tests prove the existence of high-risk HPV
- If tested positive patients are tested more frequently, a colposcopy/biopsy is performed

BUT: The tests have major weaknesses:

- The Pap-test has a high-risk of false-positive results, hence healthy patients are examined more often as necessary
- The hrHPV DNA test does not discriminate between transient infections. Most of the time the virus disappears itself: unnecessary follow up tests are performed

Follow up examinations on positive results are done too often, although they cause:

- Mental stress for patients
- Uncomfortable examinations
- Expensive treatment

Urgent need for new testing to avoid unnecessary follow-up intensive examination

Mikrogen has developed the HPV E7 test which detects evidence for CxCa more specifically and reduces the quantity of follow-up examinations

HYPOTHESE:

- E7 protein is necessary to directly inactivate cellular tumor suppressors
- E7 protein levels are high in cervical cancer
- E7 proteins are marker for cervical cancer

ASSIGNMENT:

- Detect E7 proteins or hrHPV types in cervical smears
- Key diagnostic tool: Rabbit monoclonal antibodies (RabMabs) against E7 proteins
- Quantification of E7 protein levels in conventional pap smears via sandwich ELISA

RESULT:

- Instead of identifying the hrHPV, the HPV E7 test identifies viral oncoprotein which drive cervical carcinogenesis
- Unlike the common Pap/HPV DNA test combination the Mikrogen test identifies patients who have a real risk of hrHPV induced cancer
- Hence only patients who really need it are further examined

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Figure 2: Unique Selling Proposition (USP) of PIPAWELL diagnostic kits

Upcoming Developments Hold Major Chances for Mikrogen's New HPV Test

UNMET MEDICAL NEEDS:

Quantification of a viral burden has proven to be critical in the determination of applying the correct treatment for the patient

- Current testing methods, while reliable in detecting the presence of HPV infection, are unreliable in terms of predicting the likelihood of a patient developing cervical cancer
- Neither Pap nor HPV tests provide definitive results for risk for cervical cancer

RISKS

- The U.S. Preventive Services Task Force claims current evidence is insufficient to assess the balance of benefits and harms of HPV testing and prefers giving Pap tests only every three years to women between 21 and 65
- Several other competitors offer advanced HPV tests as well

OPPORTUNITIES

- Association of HPV with head and neck cancer offers additional market potential
- Use of new markers (E7) provide more accurate testing results
- Strong women's lobby in US market and increased availability of HPV testing will stimulate the market

Source: Kalorama Information: World Market for Molecular Diagnostics 2013

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Figure 3: Market entry barriers and opportunities

		Europe	USA	Asien/SA
Relevant market	• Total Population	739	313	1.921
	• Women aged 20-60 years (27%)	200	85	519
Testing rate	• ASCUS Triage	2%	2%	0,1%
	• Adjunct screening	15%	40%	5%
	• Primary screening	20%	60%	6%
Total sales volume in market	• Qty. of tests	73.826.100	86.200.200	57.572.370
Calculation of Mikrogen sales	• Average market share Mikrogen	0,86%	0,71%	0,92%
	• Price per test	10 €	15 €	10 €
	• Years in market	12	8	11
Total Sales (in Mio. EUR)		76,2	73,4	58,3
				207,9

Figure 4: Projected PIPAWELL sales over 14 years

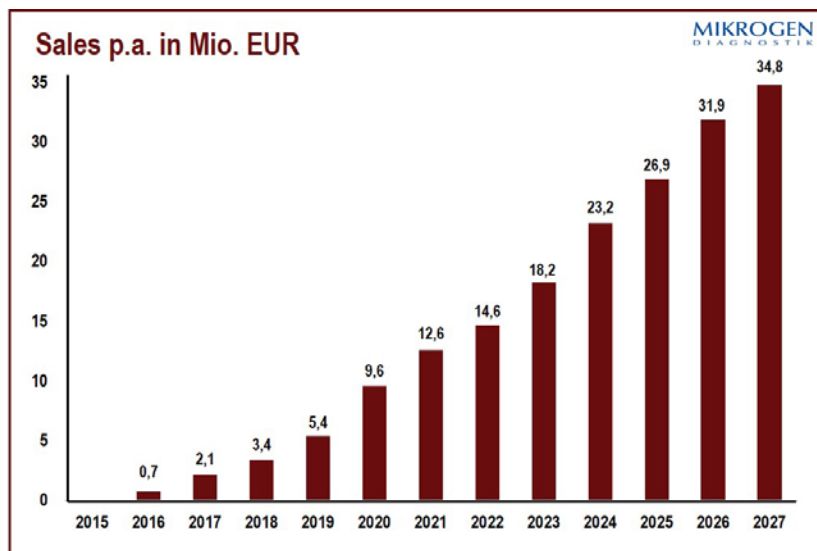


Figure 5: PIPAWELL sales projections for 2016-2017

Calculations of Sales & Marketing, G&A, R&D		
	Total expenses	Avg. annual expenses
Sales & Marketing <ul style="list-style-type: none"> Sales Force: According to regional expansion and sales development the sales team will be ramped up to 6 FTE until 2020 (Average 4,6 FTE à 70 k€). Marketing Team: While 1 FTE is to support the pre-launch phase the marketing team will be consequently enlarged to a staffing of 4 FTE until 2020 (Average 3,1 FTE à 60 k€). Marketing material: While web and PR expenses run relatively flat over the years (42,5 k€ p.a.), we expect high expenses for Fairs&Congresses in the years of market entry until 2020 (Average 56 k€). 	4.515 k€	322 k€
General & Administration <ul style="list-style-type: none"> We calculate a flat contribution rate of the project for general and administrative cost to HQ (150 k€ p.a.). 	2.100 k€	150 k€
Research & Development <ul style="list-style-type: none"> Project Lead: The project lead position will be cut down from 1,0 FTE à 90 k€ to 0,5 FTE after global roll out. Project Team: The project team will be subsequently reduced from 4 FTE à 60 k€ (during introduction phase) to 2 FTE (steady state). Contract R&D: External R&D services are planned at 500 k€ p.a. until first market entry 2016 and will then be gradually reduced to 150 k€ annually. 	2.280 k€	163 k€
	6.586 k€	472 k€

Figure 6: Calculations of Sales&Marketing, G&A, R&D

The Calculated Business Case HPV Attains a Net Present Value of About 22,9 Mio. EUR within 14 Years		
Business Case Overview		
<ul style="list-style-type: none"> Project Title: HPV testing – Screening well Project Number: MG-HPV-CxCa-001 Project Description: Mikrogen has developed the HPV E7 test which detects evidence for CxCa more specifically and reduces the quantity of follow up examinations 		
Underlying Data	Period of years	# of years
Business Case Total	2014-2027	14
Time in Market		
Europe	2016-2027	12
Asia/SA*	2017-2027	11
USA	2020-2027	8
Interest Rate		18,0%
Internal Rate of Return		66,8%
Business Case P&L (cumulated in Mio. EUR)		
Sales		207,9
Grants		1,1
COGS		16,1
Royalties		15,0
Sales&Marketing		8,5
General&Administration		2,1
Research&Development		6,6
Investment, Projects		10,5
Cash Flow		160,0
NPV@18% Int. Rate		22,9

* Asia/SA: Brasil, Mexico, Argentina, Colombia, Peru, Venezuela, China, Japan

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Figure 7: Business Case Overview

4.1.5 The address of the project public website, if applicable as well as relevant contact details.

www.pipavir.com

Annex I: List of participants and contact details

Beneficiary Number	Beneficiary name	Beneficiary short name	Country	Date enter project	Date exit project
1 (CO)	Universitaet Innsbruck PI: Pidder Jansen-Dürr Tel.: +43 512 507 50844 pidder.jansen-duerr@uibk.ac.at	UIBK	Austria	1	36
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5	Aristotelio Panepistimio Thessalonikis PI: Theodoros Agorastos Tel.: +30 2310 892140 agorast@auth.gr	AUTH	Greece	1	36
6	Oesterreichische Akademie der Wissenschaften	OEAW	Austria	1	1

Figures relating to Description of the main S&T results/foregrounds

Work Package 2

Parameter	Achieved (Yes/No)	Comments
Test format choice	Yes	“uncommon” Immunochromatography with a liquid conjugate allowing a sample/conjugate pre-incubation for better sensitivity
Antibodies conjugation to particles	Yes	Validation of RabMab Klon 42-3 and 143-7 for HPV16, 18 and 45-E7 detection Validation of the use of Gold particles amongst various markers (Biotin, Latex beads, HRP-Magnetic, etc)
Reproducibility of conjugation	Yes	Validated with all available batches of antibodies from different supplier
Membrane choice	Yes	Test of various porosity → 8µm porosity chosen
Test calibration	Yes	Validation of a mix of Goat 1 and 2 (Affinity + G200 purified) for test line and of Goat anti-Rabbit in Control line
Test protocol	Yes	Validation of two buffers: the Buffer A and B and a upgraded version for the buffer with the addition of two chemical components in buffer B to help migration of problematic samples

Table: Resume of rapid test development task:

Antigen	1st test version	Improved test version
HPV16-E7	1 ng/mL	0,1 ng/mL
HPV18-E7	1 ng/mL	0,1 ng/mL
HeLa cell lysis	25 000 cells/test	5 000 cells/test

Table: Comparison of the detection limits before and after improvement.

Study	2nd smears	1st smears
Cure CxCa	9	12
Cure HSIL	485	463
Screening	627	1577
Self Sampling	189	190
Triage Cyto+	166	180
Triage HPV+	98	289
	1574	2917

Table: number of samples tested with the rapid test per Study.

Parameter	Achieved (Yes/No)	Comments
Self-sampling buffer	No	Due to other technical problems during the hrE7-Rapid test development this has not been investigated

Development of self-sampling test (below)

Antigen	Detection limit (ng/mL)
Recombinant HPV-16 E7	1-5
Recombinant HPV-18 E7	0.5
Recombinant HPV-45 E7	1-5
Recombinant HPV-11 E7	100
Recombinant HPV-33 E7	Not detected
Recombinant HPV-35 E7	1000
Recombinant HPV-51 E7	1000
Recombinant HPV-52 E7	Not detected
Recombinant HPV-56 E7	1000
Recombinant HPV-58 E7	Not detected
Recombinant HPV-59 E7	10

Cell name	HPV type	Detection limit (cells/test)
Caski	16	100 000
SiHa	16	Not detected
HeLa	18	10 000
MS 751	45	25 000
MS 180	Other	Not detected
Cerv 215	45	25 000
C33a	Negative	Not detected