

\*\*\*\*Updated December 2016\*\*\*\*

## MarketVIEW: HPV therapeutic vaccines (CAT: VAMV050)

<b>Product Name</b>	:	<b>MarketVIEW: HPV therapeutic vaccines</b>
<b>Description</b>	:	Global vaccine commercial opportunity assessment
<b>Contents</b>	:	Executive presentation (.pdf) + 1 forecast model (.xls)
<b>Therapeutic Area</b>	:	Novel/cancer vaccines
<b>Publication date</b>	:	December 2016
<b>Catalogue No</b>	:	VAMV050

## Background

**Human papilloma viruses (HPV)**, members of the *papillomaviridae* family are extremely common with an estimated worldwide prevalence of ~11-12%. Although nearly all sexually-active men and women acquire the virus at some point in their lives, most infections are asymptomatic and self-limiting; with 90% clearing within 2 years. High risk forms of HPV (16/18) can cause changes in the cells lining the mouth, throat or anogenital tract (including the cervix); called dysplasia and can lead to cancer. All (100%) of cervical cancers are thought to be caused by HPV which is thought to be responsible for 610,000 cancers worldwide.

Two prophylactic vaccines against HPV are currently licensed (Gardasil/Merck & Co & Cervarix/GSK Biologicals). Despite their deployment, it is estimated it would take approximately 20 yrs from the implementation of mass vaccination for preventative vaccines to impact cervical cancer rates. In addition, in most HPV associated malignancies, genomic integration of the virus has already occurred necessitating a different mechanism of action for a HPV therapeutic vaccine.

Currently there are several HPV therapeutic vaccines in clinical development targeting established cancers and neoplasias such as CIN2/3. In the latter proof of clinical concept i.e. lesion regression/clearance has been shown (Inovio, VGX-3100). Larger players such as AstraZeneca/MedImmune have recently entered the field.

This **MarketVIEW** product is a comprehensive commercial opportunity assessment detailing the potential market for HPV therapeutic vaccine(s) using a patient based value/volume forecast for major Western markets to 2035. Two target product profiles (TPP) are forecasted targeting neoplasias: HPV16/18+ CIN, AIN, PIN, VIN & VAIN and HPV16/18+ established cancers – recurrent/persistent cervical cancer, oropharyngeal cancer and anal cancer. The analysis also includes an up-to-date review of epidemiology/guidelines/classifications, discussion of pricing considerations/cos effectiveness and an overview of current research and development in the field.

## Methodology

**VacZine Analytics** has closely monitored all significant source material pertaining to HPV. Example, secondary source materials used are literature articles, government websites/databases, medical bodies and associations, conference proceedings and previously analyses (where publically available). Previously published research by **VacZine Analytics** in field of novel vaccines has also been utilised. **\*\*\*See Bibliography for exact sources.**

### PRODUCT CONTENTS:

**Published December 2016 (CAT No: VAMV050)**

\*\*\*\*This product is composed of a model (.xls)<sup>1</sup> and summary presentation (.pdf)

#### Contents – Summary presentation (.pdf)

Authors Note

Executive summary

Commercial model: key outputs

HPV TX vaccine: potential revenues per indication (cancers) to 2035

HPV TX vaccine: potential volumes per indication (cancers) to 2035

HPV TX vaccine: potential revenues - cervical/per country to 2035

HPV TX vaccine: potential revenues - oral male/per country to 2035

HPV TX vaccine: potential revenues - oral female/per country to 2035

HPV TX vaccine: potential revenues - neoplasias to 2035

HPV TX vaccine: potential volumes per indication (neoplasias) to 2035

HPV TX vaccine: potential revenues by country (CIN2/3) to 2035

HPV TX vaccine: price sensitivity analysis (cancers)

HPV TX vaccine: price sensitivity analysis (CIN2/3)

HPV TX vaccine: US coverage sensitivity analysis (CIN2/3)

Human papillomavirus: disease background

What is the human papillomavirus (HPV)?

Transmission of HPV and consequences of infection

Prevalence of HPV

Worldwide prevalence of HPV

The role of HPV in human cancers

Oncogenic mechanisms of HPV

HPV-related cancers

HPV is responsible for a large proportion of global cancers

The proportion of each cancer that can be attributed to HPV varies by cancer

HPV-related cancers divided by cancer type

5 year observed survival rate of HPV-related cancers

HPV-related cancers: disease background

Cervical cancer – background

Pathogenesis of cervical cancer

IARC meta-analysis of type-specific HPV DNA prevalence in invasive cervical cancer

Cervical cancer screening programmes

---

<sup>1</sup> MS Excel model contents available on request

**Continued.....**

Cervical cancer screening - proportions of population screened  
Cervical cancer and HPV prophylactic vaccines  
HPV prophylactic vaccine schedules  
Cervical cancer – incidence  
Pre-cancerous cervical lesions  
Incidence of pre-cancerous cervical lesions and attribution to HPV  
Cervical cancer - current trends  
Cervical cancer - outlook in the era of HPV prophylactic vaccination  
Models predicting cancer incidence following HPV prophylactic vaccination  
Model predicting cancer incidence and mortality following HPV prophylactic vaccination with 2vHPV/4vHPV or 9vHPV  
Oropharyngeal cancer – background  
Prevalence of HPV in cancers in various head and neck regions  
HPV-related oropharyngeal cancer - trends and epidemiology  
Oropharyngeal cancer and HPV  
HPV16 is the most prevalent type in oropharyngeal cancer  
Oropharyngeal cancer - modelling considerations for therapeutic vaccine  
Oropharyngeal cancer – incidence  
Trends in oropharyngeal cancer incidence, cancers attributable to HPV and stage at diagnosis  
Anal cancer – background  
Anal cancer – incidence  
Pre-cancerous anal lesions – incidence  
Attribution of anal cancer and AIN to HPV and HPV type  
Anal cancer – outlook  
Penile cancer – background  
Penile cancer – incidence  
Pre-cancerous penile lesions – incidence  
Outlook for pre-cancerous penile lesions  
Vulvar cancer – background  
Vulvar cancer – incidence  
Pre-cancerous vulvar lesions – incidence  
Outlook for vulvar cancer and pre-cancerous vulvar lesions  
Vaginal cancer – background  
Vaginal cancer – incidence  
Pre-cancerous vaginal lesions – incidence  
Outlook for vaginal cancers and VAIN  
Treatment of HPV-related cancers: Current strategies  
Current treatment of CIN and cervical carcinoma in situ  
Current treatment of cervical cancer  
Current treatment of oropharyngeal cancer  
Treatment of other anogenital cancers  
Human papillomavirus therapeutic vaccines: Overview of current R&D  
The need for a HPV therapeutic vaccine  
Therapeutic vaccine against HPV – background  
Comparison of mechanism of action of prophylactic and therapeutic HPV vaccines  
Examples of immune and clinical responses to HPV vaccines  
Notable HPV therapeutic vaccines in current/past development  
Vaccines in development - MVA E2  
Vaccines in development - ADXS11-001  
Vaccines in development - ISA101/HPV16-SLP  
Vaccines in development - VGX-3100 and INO-3112

**Continued.....**

Vaccines in development - GX-188E  
Vaccines in development - GTL001 (ProCervix) and GTL002  
Vaccines in development - pNGVL4a series  
Notable HPV therapeutic vaccines no longer in development  
Ongoing HPV therapeutic vaccine trials on Clinicaltrials.gov (1) - ADXS11-001  
Ongoing HPV therapeutic vaccine trials on Clinicaltrials.gov (2) - ISA101, INO-3112 and PepCan  
Ongoing HPV therapeutic vaccine trials on Clinicaltrials.gov (3) - GX-188E and others  
HPV therapeutic vaccines: summary of progress so far  
Human papillomavirus therapeutic vaccines: Modelling commercial potential  
Commercial considerations for a therapeutic HPV vaccine  
Therapeutic HPV vaccine: target product profile (TPP)  
Modelling strategy: indications and countries  
Modelling strategy: populations/target groups  
Model assumptions: incidence/prevalence of target precancerous lesions/cancers  
CIN inputs to commercial model (20-65 yrs females)  
Model assumptions: growth rates applied/precancerous lesions/cancers  
Model assumptions: HPV 16/18+ prevalence within target precancerous lesions/cancers  
Other indication specific model assumptions  
HPV therapeutic vaccine (TX): model assumptions  
Model assumptions: first dose HPV TX vaccine penetration rates  
Model assumptions: 2nd/3rd/booster dose compliance rates  
Cost effectiveness of HPV TX vaccine  
HPV TX vaccine (s): pricing considerations  
Model validations (US): cancers  
Model validations: PAP screening  
Model validations: CIN  
Model caveats and limitations  
Appendix I: CIN treatment – review of costs  
Bibliography  
Disclaimer  
About **VacZine Analytics**

**PAGES: 144 fully referenced/sourced. Available in .pdf form**

## PRODUCT COST:

**VacZine Analytics** will grant a [enter region] license to [enter client name], for the price of:

- FULL PRODUCT - USD **\$10995.00**/ GBP **£9,160.00**# (Region license)\*
- PRESENTATION OR MODEL ONLY - USD **\$7695.00** (Region license)\*

# Indicative rate only. Prevailing rate applied to date of transaction.

\*A region is North America, Europe or ROW

For orders in the UK, VAT at 20.0% will be added to final invoice total  
*Agency/consultancy rates (commercial use) are available upon request*

## HOW TO ORDER:

To order please contact your region account manager or order direct at [orders@vaczine-analytics.com](mailto:orders@vaczine-analytics.com)  
This report can also be purchased on-line. Please review the **TERMS and CONDITIONS** of purchase.



**VacZine Analytics (R)** is a trading division of Assay Advantage Ltd, UK Company Number: 5807728

**VacZine Analytics (R)** and the “spiral logo” are UK Registered Trademarks, 2009

## BIBLIOGRAPHY:

1. McLaughlin-Drubin ME, et al. Cancer associated human papillomaviruses. *Curr Opin Virol* 2012;2(4):459-66.
2. Doorbar J, et al. The biology and life-cycle of human papillomaviruses. *Vaccine*. 2012;30S:F55-F70.
3. Cancer Research UK. What is the HPV virus? 2013. Available at: <http://www.cancerresearchuk.org/cancer-help/about-cancer/cancer-questions/what-is-the-hpv-virus> Accessed November 2016.
4. Centers for Disease Control. Genital HPV Infection - Fact Sheet. 2013. Available at: <http://www.cdc.gov/std/hpv/stdfact-hpv.htm> Accessed November 2016.
5. Forman D, et al. Global burden of human papillomavirus and related diseases. *Vaccine*. 2012;30S:F12-F23.
6. IARC monographs on the evaluation of carcinogenic risks to humans. 2012, 100B, Human Papillomaviruses. Available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/mono100B-11.pdf> Accessed November 2016.
7. Bouvard V, et al. A review of human carcinogens--Part B: biological agents. *Lancet Oncol*. 2009;10(4):321-2.
8. Kawana K, et al. Therapeutic human papillomavirus (HPV) vaccines: a novel approach. *Open Virol J*. 2012;6(Suppl 2: M21):264-9.
9. Chung CH & Gillison ML. Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications. *Clin Cancer Res*. 2009;15:6758-62.
10. Bae JM & Kim EH. Human papillomavirus infection and risk of lung cancer in never-smokers and women: an 'adaptive' meta-analysis. *Epidemiol Health*. 2015;37:e2015052.
11. Bae JM & Kim EH. Human papillomavirus infection and risk of breast cancer: a meta-analysis of case-control studies. *Infect Agents Cancer*. 2016;11:14.
12. Bae JM. Human papillomavirus 16 infection as a potential risk factor for prostate cancer: an adaptive meta-analysis. *Epidemiol Health*. 2015;37:e2015005.
13. Chahoud J, et al. Association Between  $\beta$ -Genus Human Papillomavirus and Cutaneous Squamous Cell Carcinoma in Immunocompetent Individuals-A Meta-analysis. *JAMA Dermatol*. 2015; Dec 30 [Epub ahead of print].
14. Plummer M, et al. Global burden of cancers attributable to infections in 2012: a synthetic analysis. *Lancet Glob Health* 2016;4:e609-15.
15. Giuliano AR, et al. EUROGIN 2014 Roadmap: Differences in HPV infection natural history, transmission, and HPV-related cancer incidence by gender and anatomic site of infection. *Int J Cancer*. 2015;136:2752-60.
16. American Cancer Society. 2016. Available at: <http://www.cancer.org/cancer/cervicalcancer/detailedguide/cervical-cancer-survival>. Accessed November 2016
17. Denny L. Cervical cancer: prevention and treatment. *Discov Med*. 2012;14(75):125-32.
18. Bosch FX, et al. Reframing cervical cancer prevention. Expanding the field towards prevention of human papillomavirus infections and related diseases. *Vaccine*. 2012;30S:F1-F11.
19. Ostor A et al. Natural History of Cervical Intraepithelial Neoplasia: A Critical Review. *Int J of Gynecological Pathology*. 1999 Vol 12 Issue 2
20. Anttila A et al. Cervical cancer screening policies and coverage in Europe. *Eur J Cancer*. 2009;45:2649-58
21. Cancer Research UK. Cervical cancer screening. 2013. Available at: <http://www.cancerresearchuk.org/cancer-help/type/cervical-cancer/about/cervical-cancer-screening> Accessed November 2016.
22. Centers for Disease Control and Prevention. Cervical cancer screening guidelines for average-risk women. 2012. Available at: <http://www.cdc.gov/cancer/cervical/pdf/guidelines.pdf> Accessed November 2016.
23. Canadian Task Force on Preventive Health Care. Screening for cervical cancer. 2013. Available at: <http://canadiantaskforce.ca/guidelines/screening-for-cervical-cancer/> Accessed November 2016.
24. Australian Government. National Cervical Screening Program. 2009. Available at: <http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/cervical-about> Accessed November 2016.
25. OECD. Screening, survival and mortality for cervical cancer. In OECD, Health at a Glance 2015. 2015, <http://dx.doi.org/10.1787/health-data-en>. Accessed November 2016.
26. Schiller JT et al. A review of clinical trials of human papillomavirus prophylactic vaccines. *Vaccine*. 2012;30S:F123-38.
27. Pils S & Joura EA. From the monovalent to the nine-valent HPV vaccine. *Clin Microbiol Infect*. 2015;21:827-33.
28. Sanofi Pasteur MSD. Gardasil-9 Summary of Product Characteristics. June 2016.
29. ICO (Institut Català d'Oncologia) Information Centre on HPV and Cancer. 2016. <http://www.hpvcentre.net/index.php>. Accessed November 2016.
30. Centers for Disease Control and Prevention. Recommended immunization schedule for persons aged 0 through 18 years – 2016. 2016. Available at: <http://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-schedule.pdf> Accessed November 2016.
31. Public Health Agency of Canada. Canadian Immunization Guide. 2016. Available at: <http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-hpv-vph-eng.php> Accessed November 2016.
32. Australian Government. Human papillomavirus (HPV). 2016. Available at: <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-hpv> Accessed November 2016.

33. European Centre for Disease Prevention and Control. Vaccine Schedule. 2016. Available at: <http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx> Accessed November 2016.
34. Ferlay J, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. *Eur J Cancer*. 2013;49:1374-403.
35. Cancer Today. 2016. <http://gco.iarc.fr/today/home> Accessed November 2016.
36. Holschneider CH. Cervical intraepithelial neoplasia: Definition, incidence, and pathogenesis. 2013. Available at: <http://cursoenarm.net/UPTODATE/contents/mobipreview.htm?3/62/4065/abstract/3> Accessed November 2016
37. Henk HJ, et al. Incidence and costs of cervical intraepithelial neoplasia in a US commercially insured population. *J Low Genit Tract Dis*. 2010;14:29-36.
38. Cuzick J, et al. A Population-Based Evaluation of Cervical Screening in the United States: 2008–2011. *Cancer Epidemiol Biomarkers Prev*. 2013;23(5):765-73.
39. Mayrand MH, et al. Randomized controlled trial of human papillomavirus testing versus Pap cytology in the primary screening for cervical cancer precursors: Design, methods and preliminary accrual results of the Canadian cervical cancer screening trial (CCCaST). *Int J Cancer*. 2006;119:615-23.
40. Hoyer H, et al. Cumulative 5-year diagnoses of CIN2, CIN3 or cervical cancer after concurrent high-risk HPV and cytology testing in a primary screening setting. *Int J Cancer*. 2005;116:136-43.
41. Rossi PG et al. Epidemiology and costs of cervical cancer screening and cervical dysplasia in Italy. *BMC Public Health*. 2009; 9: 71.
42. Volante R, et al. [Cervical cancer screening in Italy: quality of colposcopy and treatment. 2010 activity] *Epidemiol Prev*. 2012;36 (6) Suppl 1:78-86.
43. Castellsaque X et al. Epidemiology and costs of screening and management of precancerous lesions of the cervix in Spain. *J Low Genit Tract Dis*. 2009 Jan;13(1):38-45
44. De Sanjose S, et al. Screening of cervical cancer in Catalonia 2006–2012. *ecancer*. 2015;9:532.
45. National Health Service. NHS Cervical Screening Programme. Annual Review 2014-15.
46. Stanczuk G, et al. Clinical validation of hrHPV testing on vaginal and urine self-samples in primary cervical screening (cross-sectional results from the Papillomavirus Dumfries and Galloway—PaVDaG study). *BMJ Open*. 2016;6:e010660.
47. Bray F, et al. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. *Lancet Oncol*. 2012;13:790-801.
48. Global Burden of Disease Cancer Collaboration. The Global Burden of Cancer 2013. *JAMA Oncol*. 2015;1:505-27.
49. Drolet M, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis*. 2015;15:565-80.
50. Horn J, et al. Estimating the long-term effects of HPV vaccination in Germany. *Vaccine*. 2013;31(19):2372-80.
51. Uuskula A, et al. The epidemiological and economic impact of a quadrivalent human papillomavirus (HPV) vaccine in Estonia. *BMC Infect Dis*. 2013;13:304.
52. Kawai K, et al. Estimated health and economic impact of quadrivalent HPV (types 6/11/16/18) vaccination in Brazil using a transmission dynamic model. *BMC Infect Dis*. 2012;12:250.
53. Van de Velde N, et al. Population-level impact of the bivalent, quadrivalent, and nonavalent human papillomavirus vaccines: a model-based analysis. *J Natl Cancer Inst*. 2012;104(22):1712-23.
54. Marty R, et al. Estimating the clinical benefits of vaccinating boys and girls against HPV-related diseases in Europe. *BMC Cancer*. 2013;13:10.
55. Boiron L, et al. Estimating the cost-effectiveness profile of a universal vaccination programme with a nine-valent HPV vaccine in Austria. *BMC Infect Dis*. 2016;16:153.
56. Durham DP, et al. National- and state-level impact and cost-effectiveness of nonavalent HPV vaccination in the United States. *PNAS*. 2016;113:5107-12.
57. Chaturvedi AK. Epidemiology and clinical aspects of HPV in head and neck cancers. *Head Neck Pathol*. 2012, 6: S16-24.
58. Centers for Disease Control and Prevention. Cancers associated with human papillomavirus (HPV). 2013. Available at: [http://www.cdc.gov/cancer/hpv/basic\\_info/cancers.htm](http://www.cdc.gov/cancer/hpv/basic_info/cancers.htm) Accessed November 2016
59. Abogunrin S, et al. Prevalence of human papillomavirus in head and neck cancers in European populations: a meta-analysis. *BMC Cancer*. 2014;14:968.
60. Pytynia KB et al Epidemiology of HPV-associated oropharyngeal cancer. *Oral Oncol*. 2014 May; 50(5): 380–386.
61. D'Souza G, et al. Oral sexual behaviors associated with prevalent oral human papillomavirus infection. *J Infect Dis*. 2009;199:1263-9.
62. Gillison ML, et al. Prevalence of oral HPV Infection in the United States, 2009-2010. *JAMA*. 2012;307(7):693-703.
63. Gillison ML, et al. Epidemiology of Human Papillomavirus–Positive Head and Neck Squamous Cell Carcinoma. *J Clin Oncol*. 2015;33:3235-42.
64. Chaturvedi AK, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011;29:4294-301.

65. Kreimer AR, et al. Oral human papillomavirus in healthy individuals: a systematic review of the literature. *Sex Transm Dis*. 2010;37(6):386-91.
66. Gillison ML, et al. Human papillomavirus and diseases of the upper airway: head and neck cancer and respiratory papillomatosis. *Vaccine*. 2012;30S:F34-54.
67. Mork J, et al. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2001;344:1125-31.
68. Ang KK, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363:24-35.
69. Kreimer AR, et al. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. *Cancer Epidemiol Biomarkers Prev*. 2005;14:467-75.
70. Feller L & Lemmer J. Oral leukoplakia as it relates to HPV infection: a review. *Int J Dentistry*. 2012;2012:540561.
71. Decker Arevalo J. HPV-oropharyngeal cancer link may affect cancer screening and prognosis: The link offers potential for improved detection and prevention, but more research is needed. 2006. Available at: [http://www.enttoday.org/details/article/531945/HPV - Oropharyngeal Cancer Link May Affect Cancer Screening and Prognosis The link.html](http://www.enttoday.org/details/article/531945/HPV-Oropharyngeal-Cancer-Link-May-Affect-Cancer-Screening-and-Prognosis-The-link.html) Accessed November 2016.
72. Viens LJ, et al. Human Papillomavirus–Associated Cancers — United States, 2008–2012. *MMWR Morb Mortal Wkly Rep*. 2016;65:661-6.
73. Centers for Disease Control and Prevention. United States Cancer Statistics (USCS). Cancers By Race and Ethnicity 2009. Available at: <http://apps.nccd.cdc.gov/uscs/cancersbyraceandethnicity.aspx> Accessed August 2013.
74. Canadian Cancer Statistics. 2013. Available at: <http://www.cancer.ca/~media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/canadian-cancer-statistics-2013-EN.pdf> Accessed November 2016.
75. Cancer Research UK. Incidence cases and rates for males, females and persons in the UK, England, Wales, Scotland and Northern Ireland. 2013. Available at: [http://publications.cancerresearchuk.org/downloads/Product/CS\\_DT\\_INCCOUNTRIES.pdf](http://publications.cancerresearchuk.org/downloads/Product/CS_DT_INCCOUNTRIES.pdf) Accessed November 2016.
76. Neville BW & Day TA. Oral cancer and precancerous lesions. *CA Cancer J Clin*. 2002;52:195-215.
77. Stanley MA et al. HPV infection, anal intra-epithelial neoplasia (AIN) and anal cancer: current issues. *BMC Cancer*. 2012;12:398.
78. Moscicki AB et al. Updating the natural history of human papillomavirus and anogenital cancers. *Vaccine* 2012;30S:F24-33.
79. Australian Government. Australian Cancer Incidence and Mortality workbooks. Anal cancer for Australia. 2012. Available at: <http://www.aihw.gov.au/cancer-data/> Accessed November 2016.
80. Golden M. Anal cancer: should screening be routine? 2012. Available at: [http://depts.washington.edu/nwaetc/presentations/uploads/54/anal\\_cancer.pdf](http://depts.washington.edu/nwaetc/presentations/uploads/54/anal_cancer.pdf) Accessed November 2016
81. Wilkin T, et al. High-grade anal intraepithelial neoplasia among HIV-1-infected men screening for a multicenter clinical trial of a human papillomavirus vaccine. *HIV Clin Trials*. 2013;14(2):75-9.
82. Kreuter A, et al. Penile intraepithelial neoplasia is frequent in HIV-positive men with anal dysplasia. *J Invest Dermatol*. 2008;128:2316-24.
83. Gillison ML, et al. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. *Cancer*. 2008;113(10 Suppl):3036-46.
84. National Cancer Intelligence Network. penile cancer report: malignant and in-situ tumours: Urology SSCRG. 2013. Available at: [http://www.ncin.org.uk/cancer\\_type\\_and\\_topic\\_specific\\_work/cancer\\_type\\_specific\\_work/urological\\_cancer/urological\\_cancer\\_hub/resources](http://www.ncin.org.uk/cancer_type_and_topic_specific_work/cancer_type_specific_work/urological_cancer/urological_cancer_hub/resources) Accessed November 2016.
85. Stratton KL & Culkin DJ. A Contemporary Review of HPV and Penile Cancer. *Oncology*. 2016;30(3):245-9.
86. Baldur-Felskov B, et al. Increased incidence of penile cancer and high-grade penile intraepithelial neoplasia in Denmark 1978-2008: a nationwide population-based study. *Cancer Causes Control*. 2012;23(2):273-80.
87. Judson PL, et al. Trends in the incidence of invasive and in situ vulvar carcinoma. *Obstet. Gynecol*. 2006;107:1018-22.
88. ACOG. Management of Vulvar Intraepithelial Neoplasia, October 2016. Available at: <http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Gynecologic-Practice/Management-of-Vulvar-Intraepithelial-Neoplasia> Accessed November 2016.
89. Saunders NA, et al. Classification of vulvar intraepithelial neoplasia. *Female Patient*. 2008;33:62.
90. Van Seters M. Vulvar Intraepithelial Neoplasia: New concepts and strategy. 2008. Available at: [http://repub.eur.nl/res/pub/13147/080903\\_Seters,%20Manon%20van.pdf](http://repub.eur.nl/res/pub/13147/080903_Seters,%20Manon%20van.pdf) November 2016
91. De Vuyst H, et al. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: A meta-analysis. *Int J Cancer*. 2009;124:1626-36
92. Tatti S, et al. Anal intraepithelial lesions in women with human papillomavirus-related disease. *J Low Genit Tract Dis*. 2012;16(4):454-9.
93. Dittmer C, et al. Epidemiology of vulvar and vaginal cancer in Germany. *Arch Gynecol Obstet*. 2011;284(1):169-74.
94. Bodelon C, et al. Is the incidence of invasive vulvar cancer increasing in the United States? *Cancer Causes Control*. 2009;20(9):1779-82.



95. Andersen ES, et al. Tumours of the vagina. 2003. Available at: <http://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb4/bb4-chap6.pdf> Accessed August 2013.
96. Li H et al. Risk factors for the development of vaginal intraepithelial neoplasia. Chin Med J. 2012;125(7):1219-23.
97. Gurumurthy M & Cruickshank ME. Management of vaginal intraepithelial neoplasia. J Low Genit Tract Dis. 2012;16(3):306-12.
98. Massad LS, et al. Effect of human immunodeficiency virus infection on the prevalence and incidence of vaginal intraepithelial neoplasia. Obstet Gynecol. 2012;119(3):582-89.
99. Atay V, et al. Treatment of vaginal intraepithelial neoplasia. Cancer Ther. 2007;5:19-28.
100. Cancer Research UK. Vaginal cancer incidence statistics. 2011. Available at: <http://www.cancerresearchuk.org/cancer-info/cancerstats/types/vagina/incidence/> Accessed November 2016.
101. Cancer Research UK. Treatment if you have abnormal cervical cells. 2012. Available at: <http://www.cancerresearchuk.org/cancer-help/type/cervical-cancer/smears/treatment-if-you-have-abnormal-cervical-cells> Accessed November 2016.
102. Cancer Research UK. Curing early cervical cancer. 2012. Available at: <http://www.cancerresearchuk.org/cancer-help/type/cervical-cancer/treatment/curing-early-cervical-cancer> Accessed November 2016.
103. Cancer Research UK. Curing advanced cervical cancer. 2012. Available at: <http://www.cancerresearchuk.org/cancer-help/type/cervical-cancer/treatment/curing-advanced-cervical-cancer> Accessed November 2016.
104. Cancer Research UK. Treatment by stage for mouth cancer. 2013. Available at: <http://www.cancerresearchuk.org/cancer-help/type/mouth-cancer/treatment/types/treatment-by-stage-for-mouth-cancer> Accessed November 2016.
105. Argiris A, et al. Induction docetaxel, cisplatin, and cetuximab followed by concurrent radiotherapy, cisplatin, and cetuximab and maintenance cetuximab in patients with locally advanced head and neck cancer. J Clin Oncol. 2010;28:5294-300.
106. Kies MS, et al. Induction chemotherapy and cetuximab for locally advanced squamous cell carcinoma of the head and neck: results from a phase ii prospective trial. J Clin Oncol. 2010;28:8-14.
107. Naghavi AO, et al. Management of Oropharyngeal Cancer in the HPV Era. Cancer Control. 2016;23:197-207.
108. Cancer Research UK. Types of treatment for anal cancer. 2012. Available at: [www.cancerresearchuk.org/cancer-help/type/anal-cancer/treatment/which-treatment-for-anal-cancer](http://www.cancerresearchuk.org/cancer-help/type/anal-cancer/treatment/which-treatment-for-anal-cancer) Accessed November 2016.
109. Cancer Research UK. Types of treatment for cancer of the penis. 2012. Available at: <http://www.cancerresearchuk.org/cancer-help/type/penile-cancer/treatment/which-treatment-for-cancer-of-the-penis> Accessed November 2016.
110. Cancer Research UK. Types of treatment for vulval cancer. 2012. Available at: <http://www.cancerresearchuk.org/cancer-help/type/vulval-cancer/treatment/which-treatment-for-vulval-cancer> Accessed November 2016.
111. Cancer Research UK. Treatment by vaginal cancer stage. 2012. Available at: <http://www.cancerresearchuk.org/cancer-help/type/vaginal-cancer/treatment/types/treatment-by-vaginal-cancer-stage> Accessed November 2016.
112. Best SR, et al. Biology of HPV infection and immune therapy for HPV-related head and neck cancers. Otolaryngol Clin North Am. 2012;45(4):807-22.
113. Stern PL, et al. Therapy of human papillomavirus-related disease. Vaccine. 2012;30S:F71-82.
114. Han KT & Sin JI. DNA vaccines targeting human papillomavirus-associated diseases: progresses in animal and clinical studies. Clin Exp Vaccine Res. 2013;2:106-14.
115. Yang A, et al. Perspectives for therapeutic HPV vaccine development. J Biomed Sci. 2016;23:75.
116. Rosales R, et al. Regression of Human Papillomavirus Intraepithelial Lesions Is Induced by MVA E2 Therapeutic Vaccine. Hum Gene Ther. 2014;25:1035-49.
117. Wallecha A, et al. Lm-LLO-based immunotherapies and HPV-associated disease. J Oncol. 2012;542851.
118. Maciag PC, et al. The first clinical use of a live-attenuated *Listeria monocytogenes* vaccine: a Phase I safety study of Lm-LLO-E7 in patients with advanced carcinoma of the cervix. Vaccine. 2009;27(30):3975-83.
119. Petit R & Basu P. ADXS11-001 immunotherapy targeting HPV-E7: updated survival and safety data from a phase 2 study in Indian women with recurrent/refractory cervical cancer. J ImmunoTherapy Cancer 2013;1(Suppl 1):P231.
120. Cory L & Chu C. ADXS-HPV: A therapeutic *Listeria* vaccination targeting cervical cancers expressing the HPV E7 antigen. Hum Vaccin Immunother. 2014;10:3190-5.
121. Kenter GG, et al. Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. N Engl J Med. 2009;361:1838-47.
122. Van Poelgeest MI, et al. HPV16 synthetic long peptide (HPV16-SLP) vaccination therapy of patients with advanced or recurrent HPV16-induced gynecological carcinoma, a phase II trial. J Transl Med. 2013;11:88.
123. De Vos van Steenwijk PJ, et al. The long-term immune response after HPV16 peptide vaccination in women with low-grade pre-malignant disorders of the uterine cervix: a placebo-controlled phase II study. Cancer Immunol Immunother. 2014;63:147-60.
124. Van Poelgeest MI, et al. Vaccination against Oncoproteins of HPV16 for Noninvasive Vulvar/Vaginal Lesions: Lesion Clearance Is Related to the Strength of the T-Cell Response. Clin Cancer Res. 2016;22:2342-50.
125. ISA Pharmaceuticals. ISA101 (HPV). 2016. Available at: <http://www.isa-pharma.com/product-pipeline/product-overview/isa101-hpv/> Accessed November 2016.
126. Trimble CL, et al. Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial. Lancet. 2015;385:2078-88.

127. Kim TJ, et al. Clearance of persistent HPV infection and cervical lesion by therapeutic DNA vaccine in CIN3 patients. *Nature Commun.* 2014;5:5317.
128. Preville X, et al. Eradication of established tumors by vaccination with recombinant *Bordetella pertussis* adenylate cyclase carrying the human papillomavirus 16 E7 oncoprotein. *Cancer Res.* 2005;65:641-9.
129. Van Damme P, et al. GTL001, A Therapeutic Vaccine for Women Infected with Human Papillomavirus 16 or 18 and Normal Cervical Cytology: Results of a Phase I Clinical Trial. *Clin Cancer Res.* 2016;22:3238-48.
130. Gentcel. Gentcel reports 18 month interim analysis of GTL001 phase 2 trial in HPV16/18 infected women. 2016. <http://www.gentcel.com/news-events/news.html>. Accessed November 2016.
131. Gentcel. GTL001 – GTL002 (HPV). 2016. <http://www.gentcel.com/products/gtl001-gtl002-hpv.html>. Accessed November 2016.
132. Wu TC. Perspectives on preventive and therapeutic HPV vaccines for cervical cancer. 2010. Available at: <http://camasc.org/ppt/wu.pdf> Accessed November 2016.
133. Trimble CL, et al. A phase I trial of a human papillomavirus DNA vaccine for HPV16+ cervical intraepithelial neoplasia 2/3. *Clin Cancer Res.* 2009, 15: 361-7.
134. Maldonado L, et al. Intramuscular Therapeutic Vaccination Targeting HPV16 Induces T Cell Responses That Localize in Mucosal Lesions. *Sci Transl Med.* 2014;6:221ra13.
135. Alvarez RD, et al. A pilot study of pNGVL4a-CRT/E7(detox) for the treatment of patients with HPV16+ cervical intraepithelial neoplasia 2/3 (CIN2/3). *Gynecol Oncol.* 2016;140:245-52.
136. Daayana S et al. Phase II trial of imiquimod and HPV therapeutic vaccination in patients with vulvar intraepithelial neoplasia. *Br. J. Cancer.* 2010, 102: 1129
137. Transgene. Media releases. Available at: [http://www.transgene.fr/?page\\_id=10788](http://www.transgene.fr/?page_id=10788) Accessed November 2016.
138. Matijevic M, et al. Immunization with a poly (lactide co-glycolide) encapsulated plasmid DNA expressing antigenic regions of HPV 16 and 18 results in an increase in the precursor frequency of T cells that respond to epitopes from HPV 16, 18, 6 and 11. *Cell Immunol.* 2011;270(1):62-9.
139. UK Medicines Information. Amolimogene. 2010. Available at: [http://www.ukmi.nhs.uk/applications/ndo/record\\_view\\_open.asp?newDrugID=5217](http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=5217) Accessed November 2016.
140. Transgene corporate press release. May 9 2012. Available at: [http://www.transgene.fr/index.php?option=com\\_press\\_release&task=download&id=208&l=en](http://www.transgene.fr/index.php?option=com_press_release&task=download&id=208&l=en). Accessed November 2016.
141. US Census Bureau. International Database (IDB). Available at: <http://www.census.gov/ipc/www/idb/index.php>. Accessed August 2013.
142. Agorastos T, et al. Detection and typing of human papillomavirus DNA in uterine cervixes with coexistent grade I and grade III intraepithelial neoplasia: biologic progression or independent lesions? *Eur J Obstet Gynecol Reprod Biol.* 2005;121(1):99-103.
143. Gunderson CC, et al. A contemporary analysis of epidemiology and management of vaginal intraepithelial neoplasia. *Am J Obstet Gynecol.* 2013;208(5):410.e1-6.
144. Buscema J, et al. The predominance of human papillomavirus type 16 in vulvar neoplasia. *Obstet Gynecol.* 1988;71(4):601-6.
145. Cleveland JL, et al. The connection between human papillomavirus and oropharyngeal squamous cell carcinomas in the United States: implications for dentistry. *J Am Dent Assoc.* 2011;142(8):915-24.
146. Smith, TW. American Sexual Behavior 2006: trends, socio-demographic differences, and risk behavior. GSS topical report no. 25. Chicago: NORC.
147. Prevalence and Awareness of HIV Infection Among Men Who Have Sex With Men --- 21 Cities, United States, 2008 Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5937a2.htm>. Accessed November 2016
148. US CDC. HIV in the United States at a glance. Available at: <http://www.cdc.gov/hiv/statistics/basics/ata glance.html>. Accessed August 2013.
149. Seay J, et al. High acceptance rate of anal pap screening despite limited knowledge about anal dysplasia among HIV+ MSM. *Infect Agent Cancer.* 2010;5(Suppl 1):A31.
150. Golden M, et al. Anal cancer should screening be routine? Available at: [http://depts.washington.edu/nwaetc/presentations/uploads/54/anal\\_cancer.pdf](http://depts.washington.edu/nwaetc/presentations/uploads/54/anal_cancer.pdf). Accessed November 2016
151. Melnikow J, et al. Natural history of cervical squamous intraepithelial lesions: a meta-analysis. *Obstet Gynecol.* 1998;92:727-35
152. Wai TT, et al. Modern management of abnormal cervical smear. *BJMP.* 2008;1(2):18-22.
153. Friedlander M, et al. 2002. Guidelines for the Treatment of Recurrent and Metastatic Cervical Cancer. *The Oncologist.* 2002;7:4342-347.
154. Palefsky JM, et al. Natural History and Clinical Management of Anal Human Papillomavirus Disease in Men and Women Infected with Human Immunodeficiency Virus. *Clin Infect Dis.* 2002 ;35:1127-34.
155. Marks DK & Goldstone SE. Electrocautery Ablation of High-Grade Anal Squamous Intraepithelial Lesions in HIV-Negative and HIV-Positive Men who have sex with Men. *JAIDS.* 2011; November 30.
156. Hakenberg OW et al. European Association of Urology. Guidelines on Penile Cancer. Available at: [https://uroweb.org/wp-content/uploads/12-Penile-Cancer\\_LR.pdf](https://uroweb.org/wp-content/uploads/12-Penile-Cancer_LR.pdf) Accessed November 2016
157. Van Seters M, et al. Treatment of vulvar intraepithelial neoplasia with topical imiquimod. *N Engl J Med* 2008;358:1465-73.

158. National Cancer Institute. Vaginal Cancer Treatment. Available at: <http://www.cancer.gov/cancertopics/pdq/treatment/vaginal/HealthProfessional/page4>. Accessed November 2016
159. National Cancer Institute. General Information About Oropharyngeal Cancer. Available at: <http://www.cancer.gov/cancertopics/pdq/treatment/oropharyngeal/HealthProfessional/page1>. Accessed November 2016
160. Sesterhenn AM, et al. Cancer of the oro- and hypopharynx - when to expect recurrences? Acta Otolaryngol. 2008;128(8):925-9.
161. Luttjeboer J et al. Threshold cost-effectiveness analysis for a therapeutic vaccine against HPV-16/18-positive cervical intraepithelial neoplasia in the Netherlands. Vaccine. <http://dx.doi.org/10.1016/j.vaccine.2016.10.019> (November 2, 2016)
162. UK Parliament. HPV Vaccine. Motion made, and Question put forthwith (Standing Order No. 118(6)), 2 July 2013.
163. Human Papillomavirus Fact Sheet. Stressgen Biotechnologies. Available at: [http://www.oralcancerfoundation.org/dental/pdf/HPV\\_Fact\\_Sheet.pdf](http://www.oralcancerfoundation.org/dental/pdf/HPV_Fact_Sheet.pdf). Accessed August 2013.
164. US 2010 (National Ambulatory Medical Care Survey).
165. Canadian Women Health Network. Available at: <http://www.cwhn.ca/node/40773>. Accessed November 2016
166. Rossi PG, et al. Epidemiology and costs of cervical cancer screening and cervical dysplasia in Italy. BMC Public Health. 2009;9:71.
167. Castellsague X et al. Epidemiology and costs of screening and management of precancerous lesions of the cervix in Spain. J Low Genit Tract Dis. 2009;13(1):38-45.
168. Cervical Intraepithelial Neoplasia (CIN) (Squamous Dysplasia). Available at: [http://cdn.intechopen.com/pdfs/27770/InTech-Cervical\\_intraepithelial\\_neoplasia\\_cin\\_squamous\\_dysplasia\\_.pdf](http://cdn.intechopen.com/pdfs/27770/InTech-Cervical_intraepithelial_neoplasia_cin_squamous_dysplasia_.pdf). Accessed November 2016

**TERMS and CONDITIONS:**

VacZine Analytics – a trading division of Assay Advantage Ltd UK Company Number: 5807728 (Herein referred to as “The Company”). (Herein [enter client name] to as “The Client”).

1. This finished research product is provided is provided as a Service. Any additional Service required by the client will be subject to a new proposal being prepared.
2. The Service will commence after written (e-mail) or Fax confirmation stating the Client’s acceptance of the Service according the description proposed by the Company.
3. **Cancellation policy.** The Company’s cancellation policies are in accordance with the EU Consumer Protection (Distance Selling) Regulations 2000 (DSRs). Prior to acceptance of an order the Company will make available written information regarding Clients cancellation rights. This is posted on the Company website and is available for public review.
4. **Cancellation rights:** For finished documents - a Clients cancellation rights will last for **seven working days** counting from the day that the order was concluded. If the Services i.e. provision of the documents has taken place with the Clients agreement before this period the Client’s cancellation rights have ended.
5. Invoicing will **100%** after submission of deliverables to the Client in a form reasonably acceptable to the Client.
6. If not purchased on line invoices are payable within **thirty days** of the invoice date.
7. All proposals are quoted in **\$USD dollars or £GBP** and invoices are to be settled in the same currency.
8. The Company agrees not to disclose to any third party confidential information acquired in the course of providing the services listed without the prior written consent of the Client. Exception occurs when the information is already in the public domain or when disclosure is necessary to help the Company’s employees and agents with the performance of the Company’s obligations to achieve satisfactory completion of the project and approved in writing by the Client.
9. Force Majeure: The Company will not be liable for any delay or failure to perform any obligation under this Agreement insofar as the performance of such obligation is prevented by an event beyond our reasonable control, included by not limited to, earthquake, fire, flood or any other natural disaster, labour dispute, riot, revolution, terrorism, acts of restraint of government or regulatory authorities, failure of computer equipment and failure or delay of sources from which data is obtained.
10. Please also refer to Master **TERMS and CONDITIONS** available upon request.

**VacZine Analytics**

Warren House  
Bells Hill  
Bishops Stortford  
Herts  
CM23 2NN  
United Kingdom  
Tel: +44 (0) 1279 654514 / +44 (0) 7952470582 / Fax: +44 (0) 1279 655926  
E-mail: [info@vacZine-analytics.com](mailto:info@vacZine-analytics.com)

## About VacZine Analytics:

**VacZine Analytics** is an established strategic research agency based in the United Kingdom. Its aim is to provide disease and commercial analysis for the vaccine industry and help build the case for developing new vaccines and biologics.

For more information please visit our website [www.vacZine-analytics.com](http://www.vacZine-analytics.com)

**VacZine Analytics (R)** is a trading division of Assay Advantage Ltd, UK Company Number: 5807728

**VacZine Analytics (R)** and “the spiral logo” are UK Registered Trademarks, 2009

Follow us on Twitter [@vaccineanalytic](https://twitter.com/vaccineanalytic)

Signup to our newsletter ExpertREACT - <http://www.vacZine-analytics.com/products-expertreact.asp>