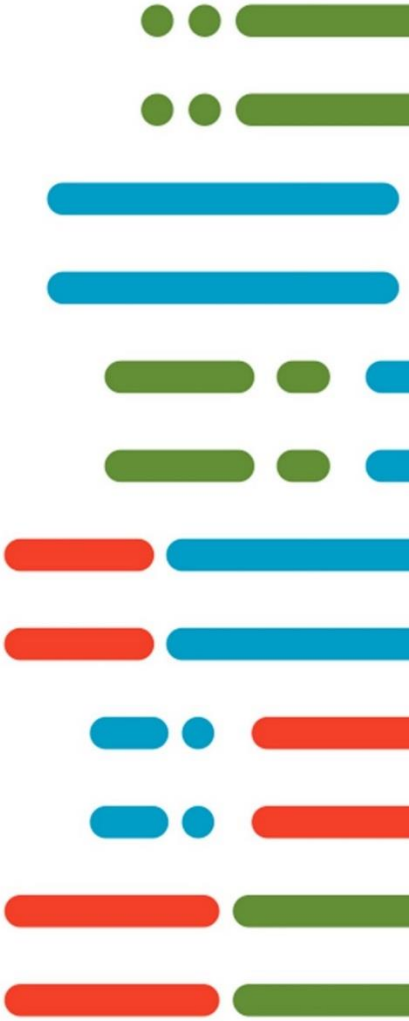
GENOMIC VISION

HPV Program



Cervical cancer is a major public health problem

- 3rd most common cancer in women
- 275.000 deaths /year in the World
- Good prognosis: 5-years survival rate is ~ 70%, 92% when followed and treated

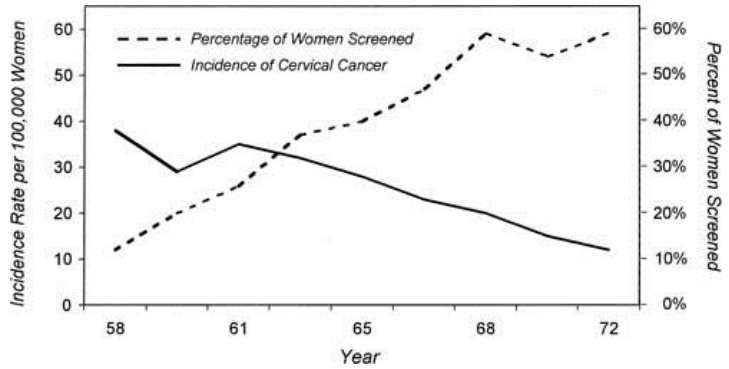
	World	U.S.	E.U	France
Incidence	530 000	75 000	31 000	3 000
Mortalité	275 000	33 000	13 000	1 000

GLOBOCAN 2008 (IARC) , *Section of Cancer Information (8/12/2012)*

Importance of Pap-smears in the cervical cancer screening

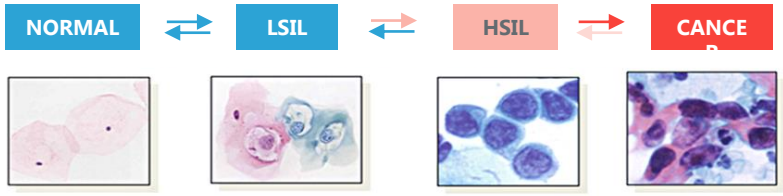
George Papanicolaou

Inventor of the "Pap smears" (1928)

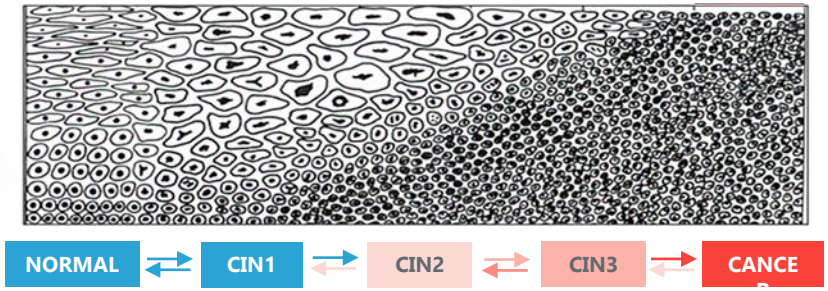


(Blavstein's Pathology of the Female Genital Tract. 5th ed. New York, Springer-Verlag, 2002.)

Pap smears: cytology



Biopsy: histology



This primary screening test has its limits:

- **Insufficient sensitivity** for the CIN2+ detection : ~53%

  → Repeatability of Pap-smears (every 2-3 years) increases the sensitivity to 70-80%
- Test operator-dependent
- **Ambiguous results are frequent** (ASCUS = 3-8%): only 5-10% of them are really associated with concurrent CIN2+

HPV infection is the major cause of cervical cancer

- Nearly 100% of cervical cancer are linked to a **persistent infection by a high-risk HPV** (Human Papillomavirus)
- 70-80% of women will get an HPV infection at some point in life.
- In 90% of cases, the body "clears" HPV with its own immunity
- > 75 different HPV genotypes
- **14 HPV strains are considered as "high risk" (HR) oncogenic isotypes**
- HPV types 16 and 18 are the most prevalent in about 70% of cervical cancer (in Caucasian population)
- **Integration of HR-HPV DNA is a critical step in the development of cervical cancer**

HR-HPV testing: a breakthrough in cervical cancer screening

Different HPV tests approved

The cobas® HPV Test (Roche) is the only clinically validated, FDA-approved assay that simultaneously provides pooled results on 14 high-risk genotypes and individual results on the highest-risk genotypes, HPV 16 and HPV 18.

Hallmarks of HPV testing are:

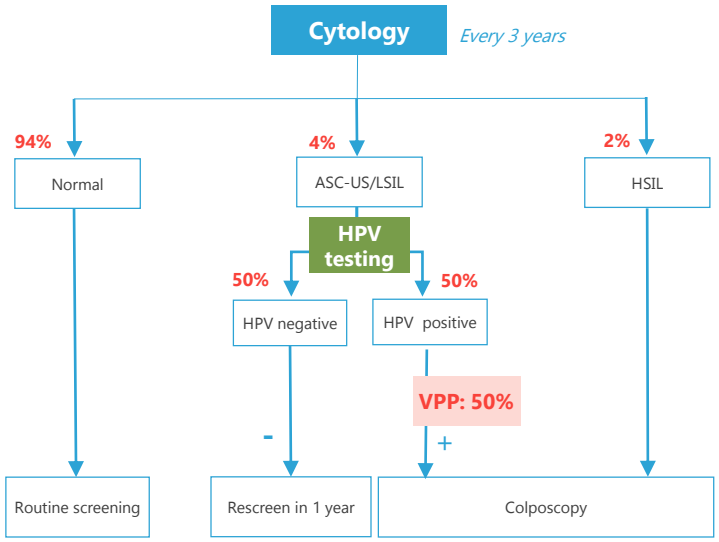
- **Higher sensitivity** than Pap smears
- **Very high NPV** : if HPV-, only 0,27% of CIN2+ risk after 5 years
- **Standardized** and automated tests : results are no operator-dependant
- But **lower specificity** than Pap smears

HPV testing and Pap-smears are complementary screening methods

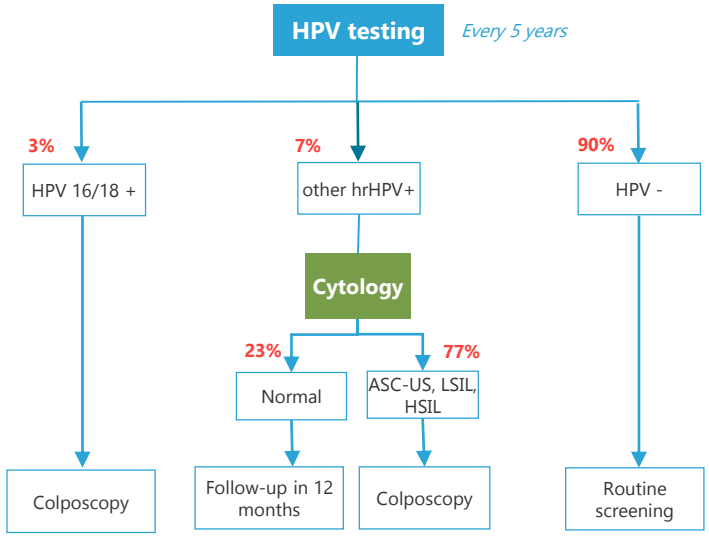
Cervical cancer screening algorithm

- No consensus in cervical cancer screening guidelines among European countries and the U.S.
- HPV tests approved by the FDA are recommended for:
  - **Triage** of women (21 to 65 years) with atypical squamous cells of undetermined significance (ASCUS) pap-smears
  - Post-therapeutic control of CIN2/3 patients
  - HPV and cytology **cotesting** for women between 30 and 65 years
  - **HPV primary screening**, triage with cytology (only for Cobas test, Roche) for women between 30 and 65 years

A **"Current" algorithm**



B **"Future" algorithm***



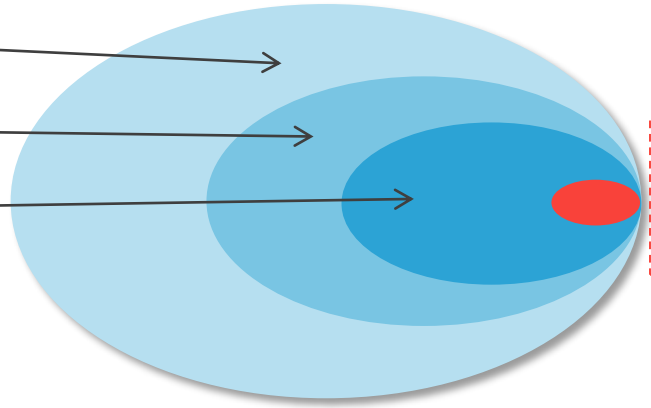
* Already used in USA, to be generalized in a short term

HPV integration: Biomarker for the triage of HPV+ women

Women sexually active

HPV infection : HPV DNA detection

E6/E7 mRNA over expression



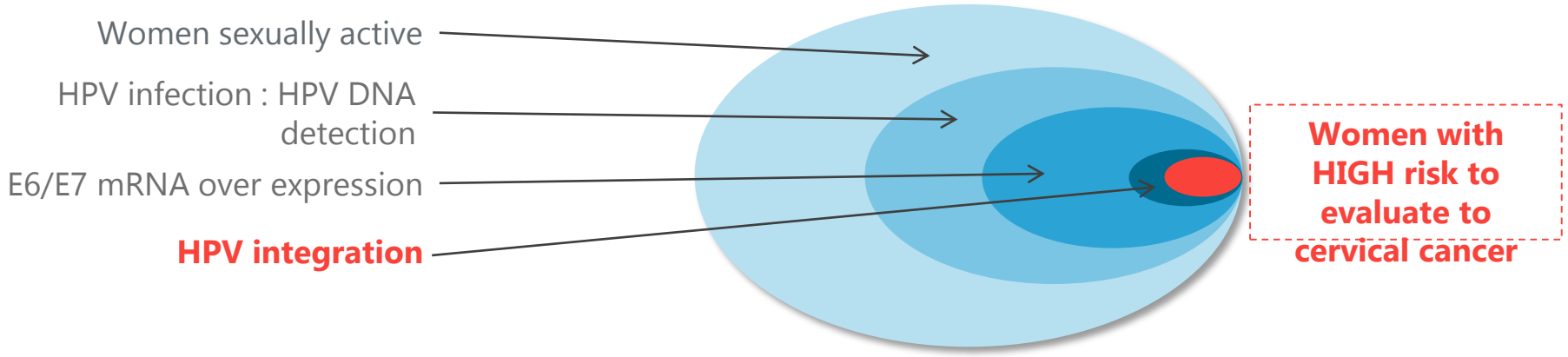
Women with HIGH risk to evaluate to cervical cancer

HPV test lack of specificity

- Useless colposcopies and follow-up
- Over-treatment
- Psychological impact
- Economic impact

Necessity of a more specific biomarker to distinguish patients with high risk to develop a cervical cancer

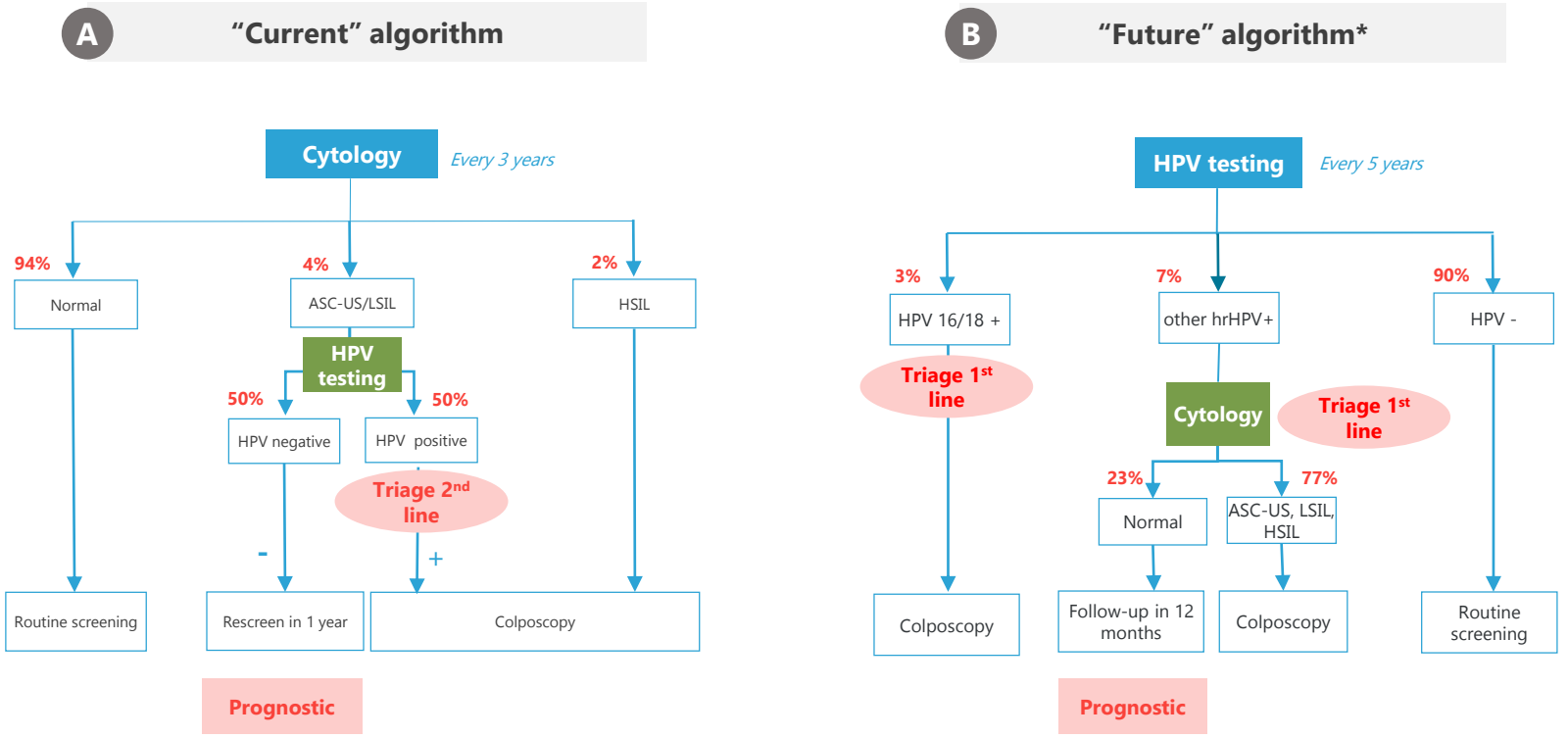
HPV integration: Biomarker for the triage of HPV+ women



Development of a Molecular Combing assay that detects directly HPV integration in the genomes of patients

Positioning of the Molecular combing HPV test

An optimal integrated screening and triage strategy



* Already used in USA, to be generalized in a short term

Objectives

HPV

DIAGNOSTIC value

Improvement of the triage of women with ASC-US or LSIL

→ Reduction of useless colposcopies

PROGNOSTIC value

Help to stratify the risk of progression to high-grade dysplasia/cancer

→ Better management and follow up of patients

HPV test technical development

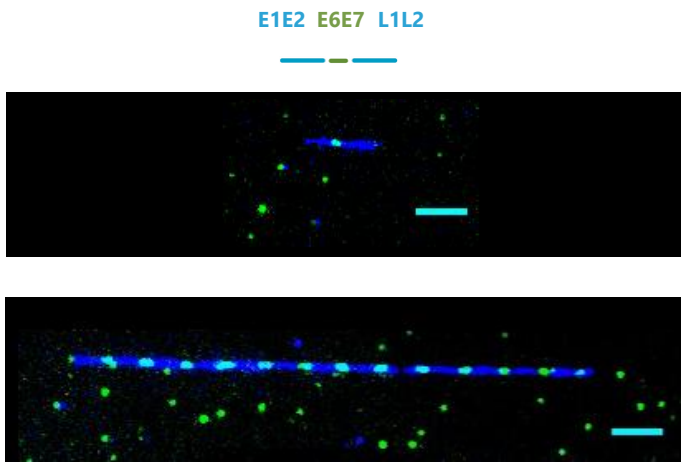
Clinical validation

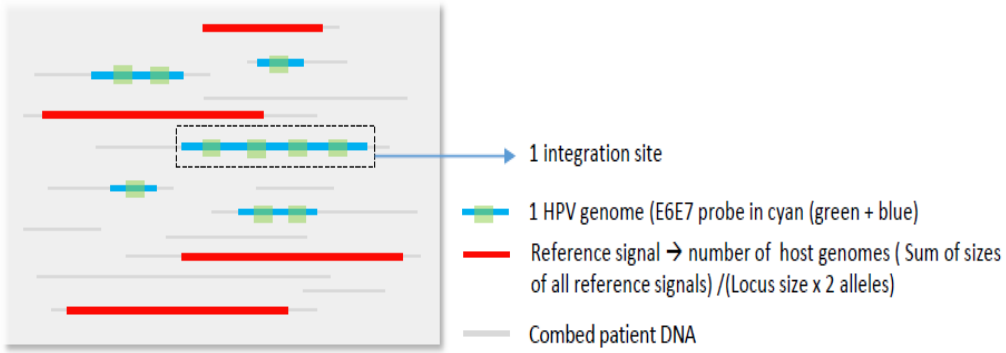
Added-value of Molecular Combing for the detection of HPV integration

- **Direct** observation of HPV genome integration
- **High-resolution**
  - Number of integration sites / patient's genome
  - Single integrations/ tandem integrations (multiples)
  - Number of HPV genomes integrated / integration site

Hybridization of fluorescent probes specific for **HPV-HR** genomes

DNA extracted from pap-smears of HPV+ patients





Clinical validation

Association between high-risk HPV genome integration detected by Molecular Combing and cervical lesions severity and/or evolution

Set-up of 2 clinical studies

- IDAHO study: 8 Hospitals involved in France

- EXPL-HPV-002: 2 clinical sites involved in CZR, one active (Dr Dvorak)
  Prague Clinical Services (PCS) in charge of the study

PRAGUE CLINICAL SERVICES

Your partner in clinical development since 2004

EXPL-HPV-002 Objectives

Principal

The aim of this study is to validate the **integration** of the HPV-HR as an appropriate biomarker of the **severity of precancerous lesions**

DIAGNOSTIC value of HPV integration

Secondary

To evaluate the pronostic performances of HPV **integration** as a biomarker of **the clearance of HPV**

To validate the **integration** of the HPV-HR as an appropriate biomarker of **progression of cervical lesions** towards cervical cancer

To evaluate the **integration rate** according to the HPV genotype

PRONOSTIC value of HPV integration

EXPL-HPV-002 Study design

- Exploratory Study
- GCP study
- Open-label
- Single arm
- Two parts:
  cross-sectional part – one study visit
  longitudinal part (follow-up) – up to 6 visits

EXPL-HPV-002 Study Endpoints

Primary Endpoint

- Integration of HPV genomes studied by molecular combing (For each patient, several parameters will be assessed during the analysis by molecular combing)
- Lesion status
- Cytological classification
- Clinical outcome of cervical lesions (only for patients in follow up)
- Viral clearance (only for patients in follow up)
- Cure (only for patients in follow up)

EXPL-HPV-002 Site selection

- Site #6

  Prof. MUDr. Pavel Ventruba, DrSc., MBA

  Gynecological – obstetric clinic

  The University Hospital Brno

- Site #5

  MUDr. Vladimír Dvořák – Co-Ordinating Investigator

  Center for outpatients gynecological and primary care, Brno

EXPL-HPV-002 Laboratories

- **Genotyping: UHKT, Dr Tachezy**
  - Samples transported from the site to the lab on weekly basis
  - Samples evaluated approximately every two weeks
  - After evaluation, HR-HPV positive samples sent to GV labs
- **Histology: Aeskulab, Dr Trnkova**
  - Samples transported on daily basis
  - Results sent to the site on regular basis; to CRO per request

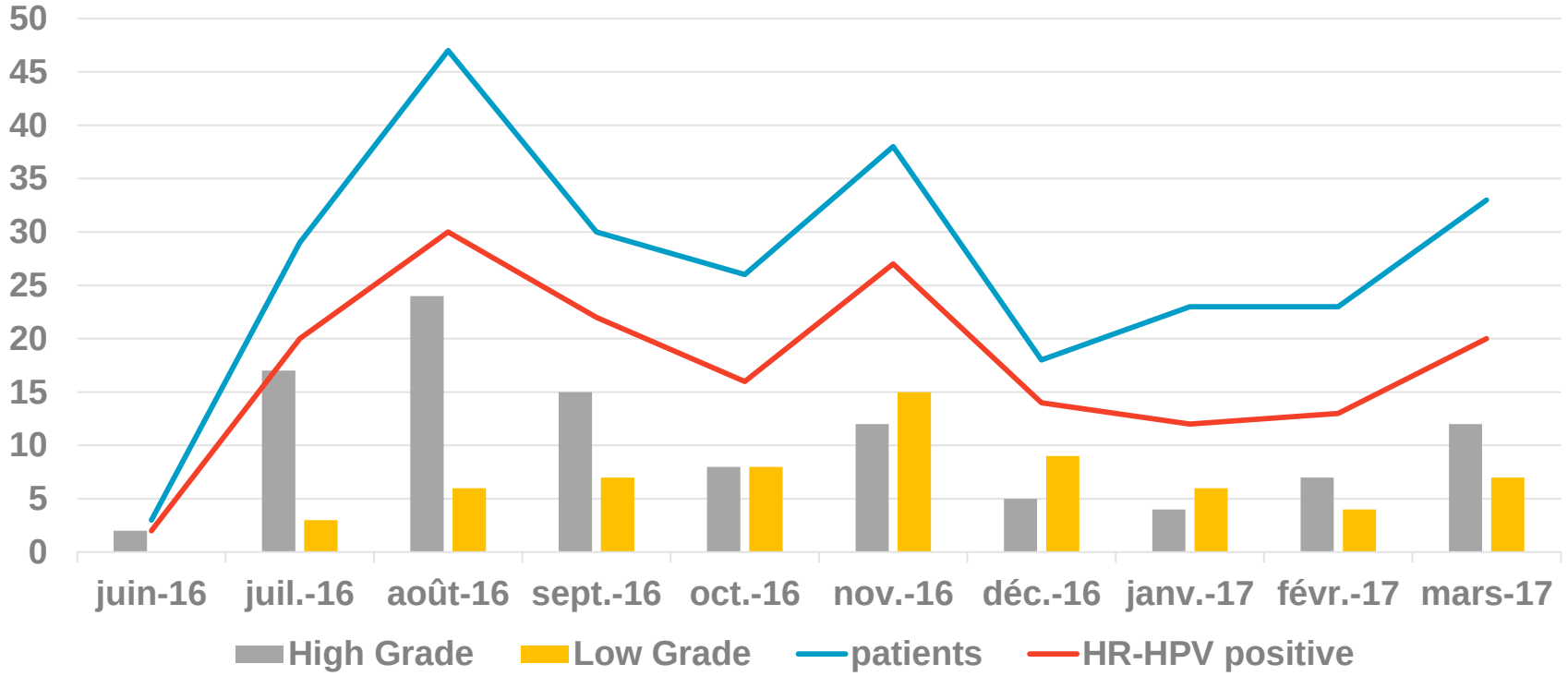
EXPL-HPV-002 Sample size

Enrolment goal: 400 subjects HR-HPV

- based on literature search concerning the primary goal:
  "association between the integration of high-risk HPV genomes and the severity of cervical lesions"

- based on distribution between HG cervical lesions and LG cervical lesions associated with HR-HPV on the main clinical site
- statistical considerations - difficult statistical calculation, limited data
- meta-analysis with the French HPV study data (IDAHO study)

EXPL-HPV-002 Recruitment details



- 303 patients recruited, 13 of them excluded by sponsor's decision because of low DNA quantity
- 289 of them evaluated for HPV positivity
- 178 samples evaluated as HR-HPV positive
  - 106 High Grade
  - 65 Low grade

EXPL-HPV-002 Interim analysis

- **Analyzed samples:**
  - Patients enrolled by the end of 2016:
  - 138 HR-HPV positive patients of 203 enrolled patients
  - 12 samples excluded (low DNA quantity)

Deleted for confidentiality reason in publicly distributed document

EXPL-HPV-002 Conclusion

- **Preliminary encouraging results: DNA combing methodology has a power to improve the current diagnostic and treatment methods in cervical cancer**
- **More robust statistical data are needed**
- **Sufficient data will be obtained by the study continuation in both cross-sectional and longitudinal phases.**