



# Relevance and importance of HPV mRNA E6/E7 biomarkers in the prevention of cervical cancer

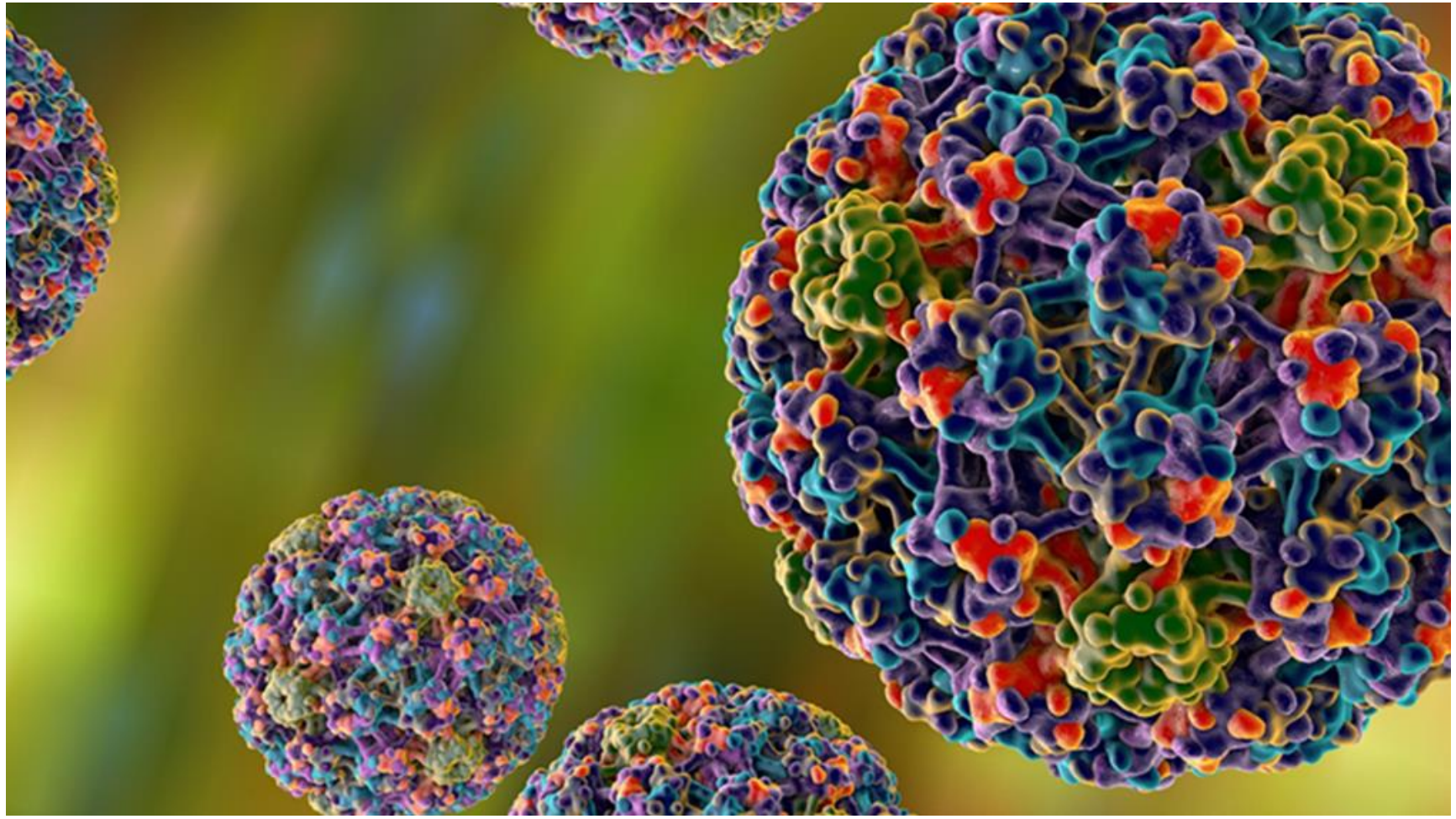
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# Prevention of cervical cancer is possible

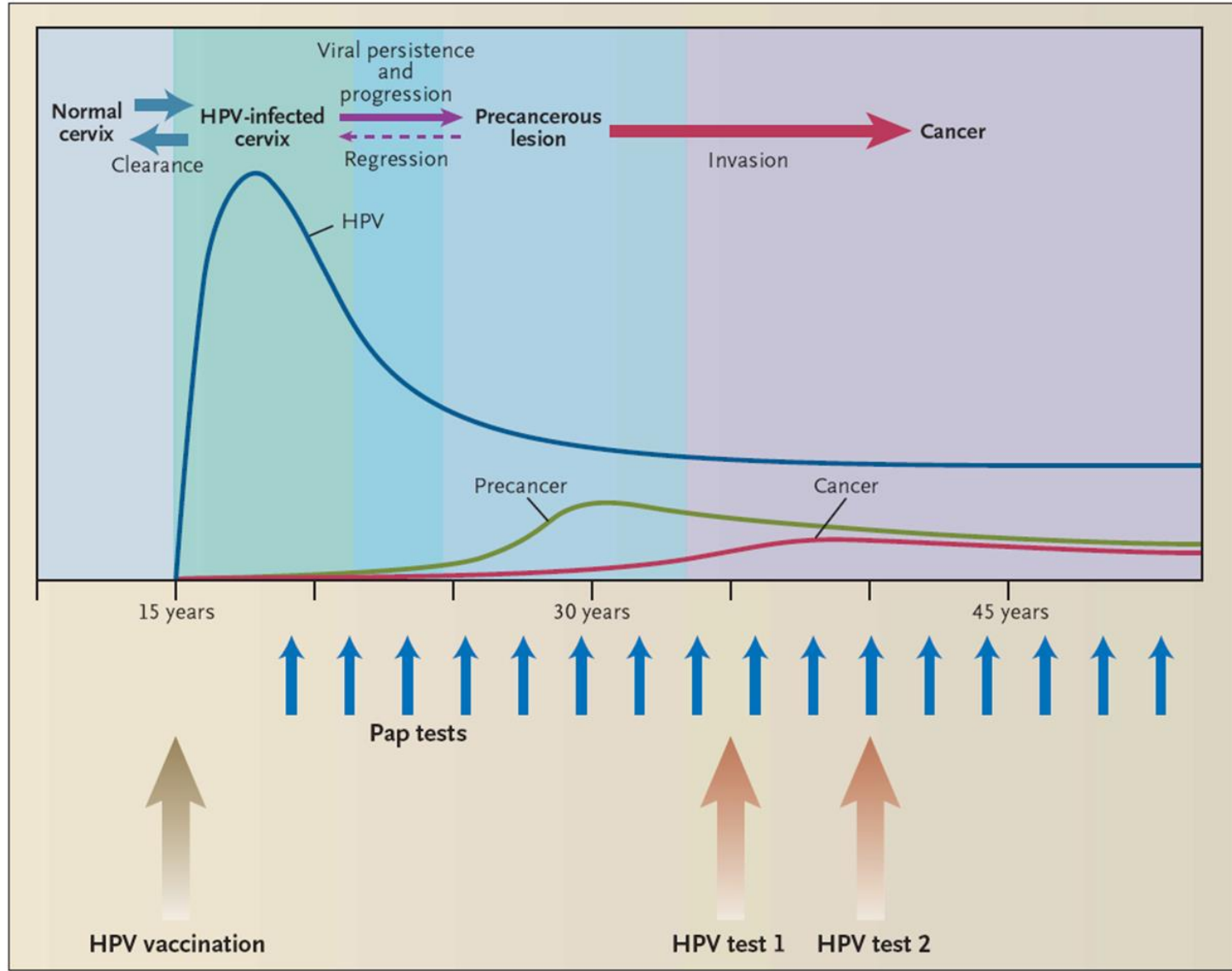
- Cervical cancer is caused by human papillomavirus (HPV) and develops over several years through a series of precancers
- HPV is a common STI, 70-80% of all women get infected during lifetime
- Most HPV infections are transient; 90% regress spontaneously within two years
- HPV testing and vaccination may eradicate Cervical cancer in future

## Development of cervical cancer

- A transient HPV-infection is not dangerous, carrying a low risk of disease
- A type specific persistent infection over 10-15 years increases risk of high grade precancer and cancer (CIN2+)
- Risk is strongly associated with certain aggressive HPV genotypes that require a closer patient management

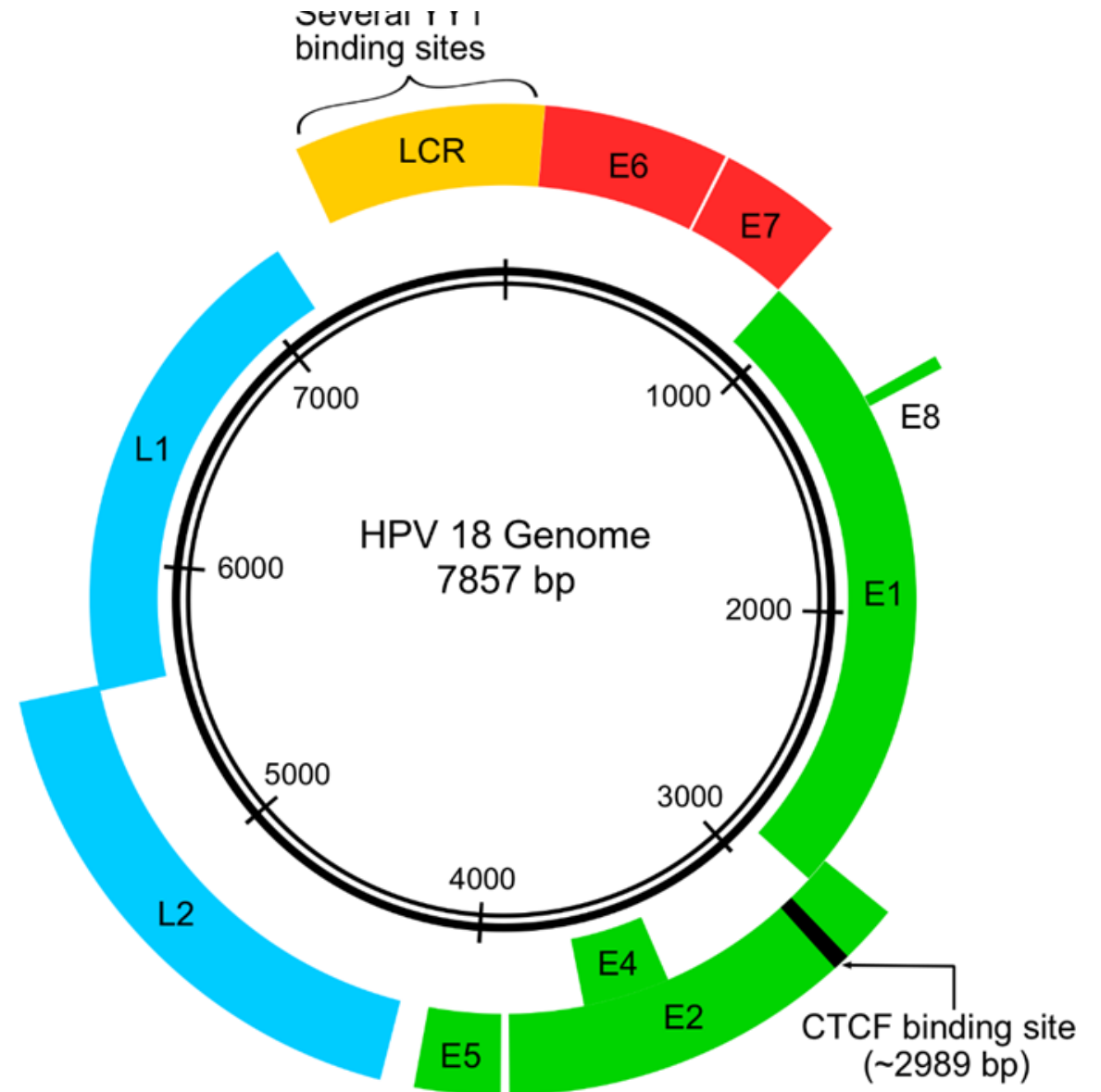


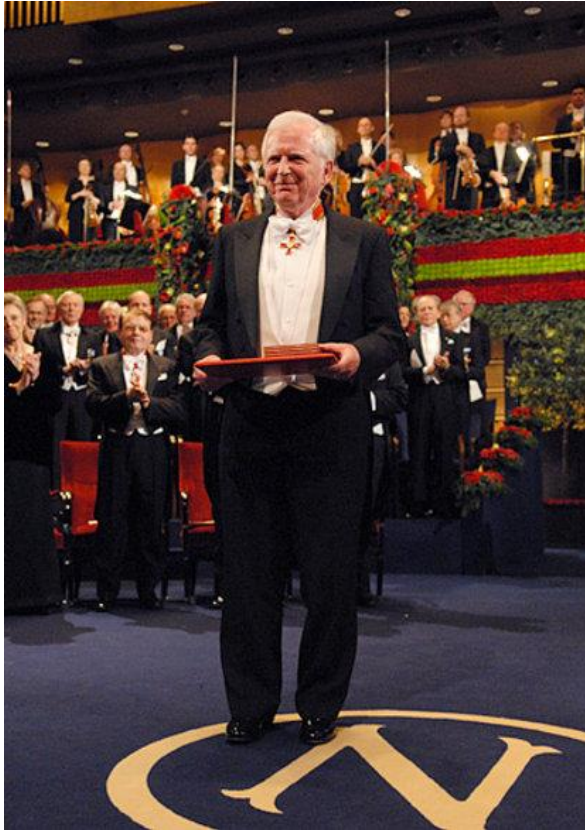




# HPV genome

- Six early (E) genes
  - regulate HPV viral replication
- Two late (L) genes
  - encode capsid proteins
  - L1 is targeted by most HPV DNA tests





## Harald zur Hausen Nobel Prize Laureate, 2008

- Discovered the link between human papilloma viruses and cervical cancer
- Demonstrated in 1983 that cervical cancer in humans is caused by certain types of papilloma viruses (wart viruses), the genes from which are incorporated into the host cells' DNA
- This discovery made it possible to develop a vaccine against cervical cancer, which had been the second most common tumor disease in women



# The cause of Cervical Cancer

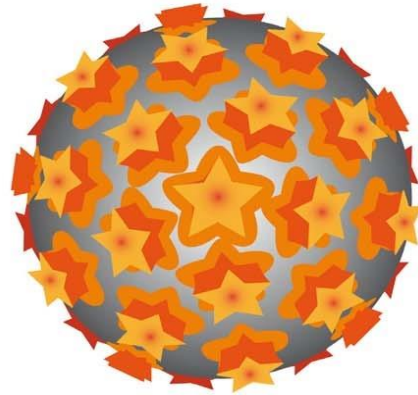
- The real cause of cervical cancer is not the HPV infection per se
- Over-expression of **E6 and E7 oncoproteins** is a critical and required step for conversion to malignancy
- An important event in carcinogenesis is the integration of the virus into the host genome which, in turn, leads to an increase in E6 and E7 expression

HPV mRNA  
E6/E7  
biomarkers

- Biomarkers E6/E7 mRNA are **precursors to E6/E7 oncoproteins**; directly relevant to disease progression by:
  - disturbance of cell cycle control,
  - deficiency in DNA repair,
  - genomic instability
  - increased risk of malignant transformation
- Detecting mRNA E6/E7 offers new opportunities to improve the effectiveness of cervical cancer screening by detecting oncogene activity and not viral presence

# The Cause of Cervical Cancer

## Different Prevention Concepts



HPV



HPV-virus testing  
identifies a  
harmless condition



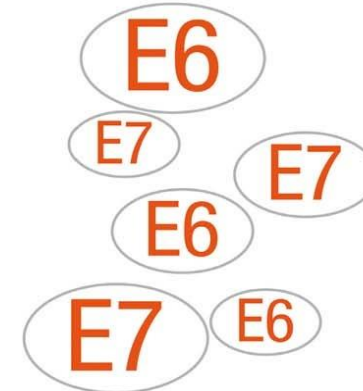
DNA indicates  
presence of  
HPV



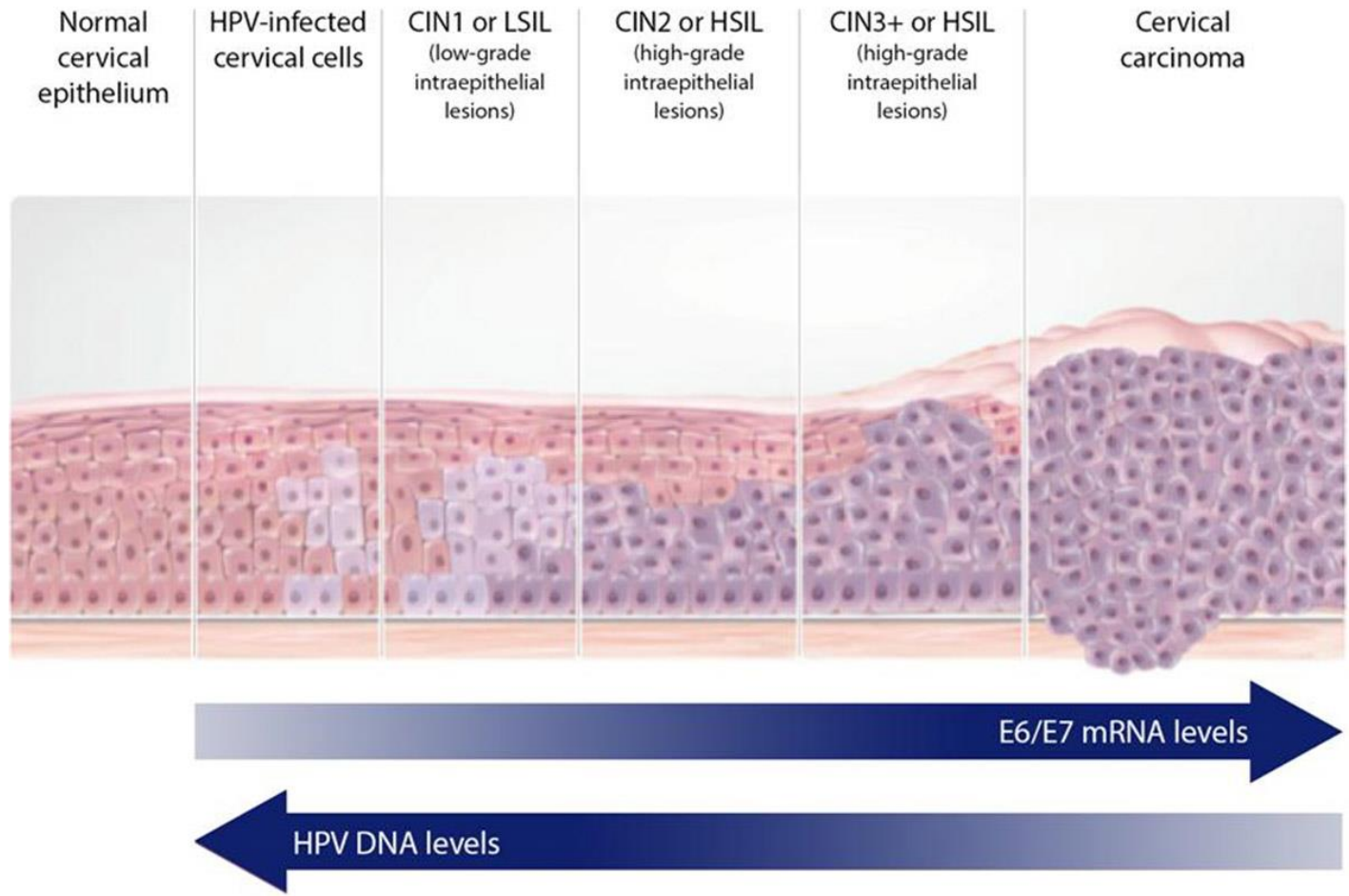
E6/E7 mRNA  
indicates activity of  
HPV oncogenes



**PreTect technology identifies  
a high risk condition**



E6/E7 oncoproteins  
induce cell  
transformation



## Diagnostic test characteristics

**Sensitivity:** The ability of a test to correctly classify an individual as "diseased"

**Specificity:** The ability of a test to correctly classify an individual as "disease-free"

**PPV:** Positive Predictive Value (true positives)

**NPV:** Negative Predictive Value (true negatives)



# Tradeoff between Sensitivity and Specificity

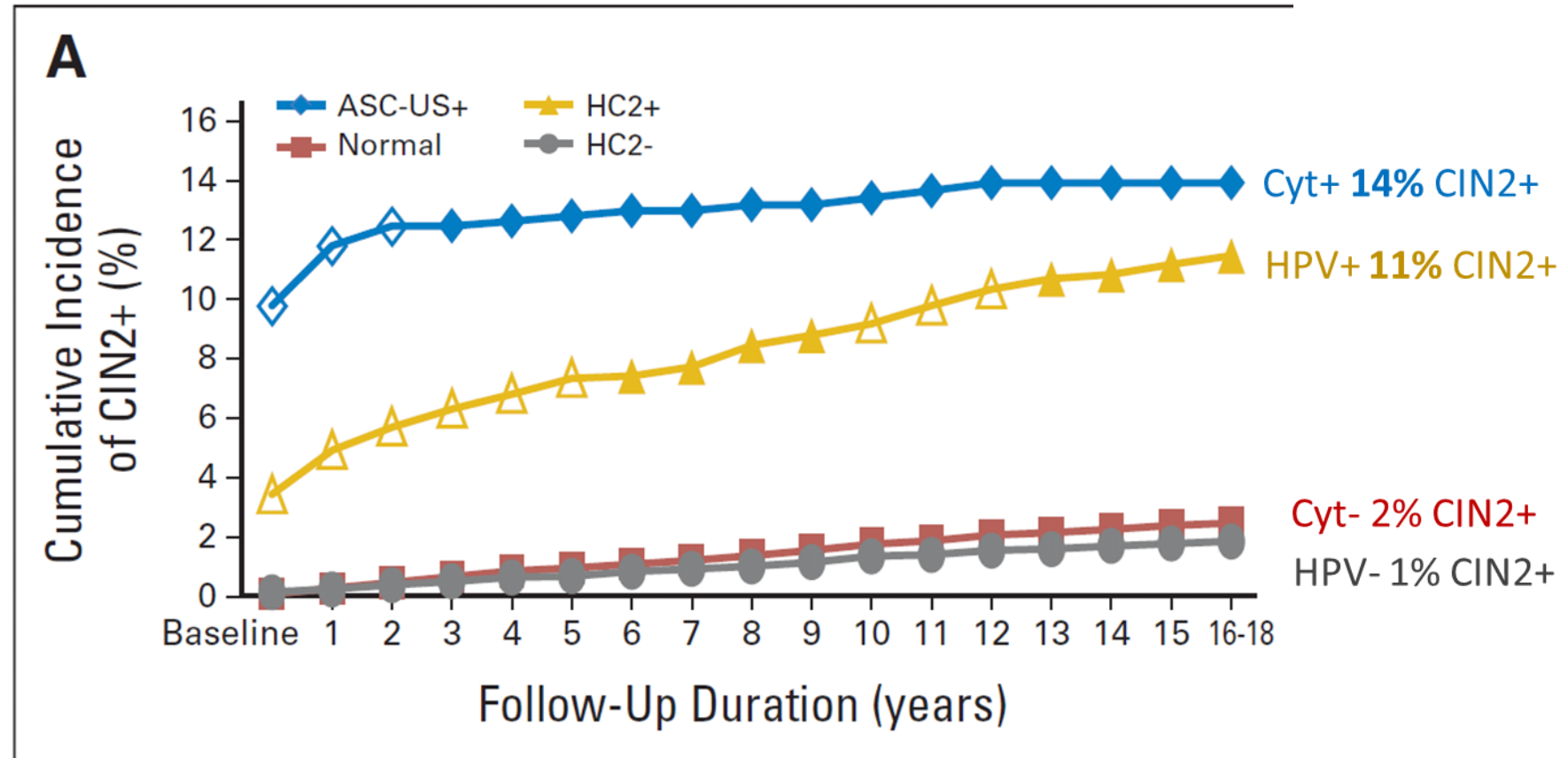
Selecting the optimal balance of sensitivity and specificity depends on the **purpose** for which the test is going to be used

- A screening test should be highly sensitive in order to **RULE OUT** those without the disease
- A confirmatory test should be highly specific in order to **RULE IN** those with the disease

# HPV DNA testing

- HPV DNA tests have excellent sensitivity for CIN2 or higher, but specificity is low (false positives)
- Since most women have self-resolving HPV infections that will not develop into cancer, a positive HPV DNA test result provides little actionable information

## HPV DNA versus Cytology

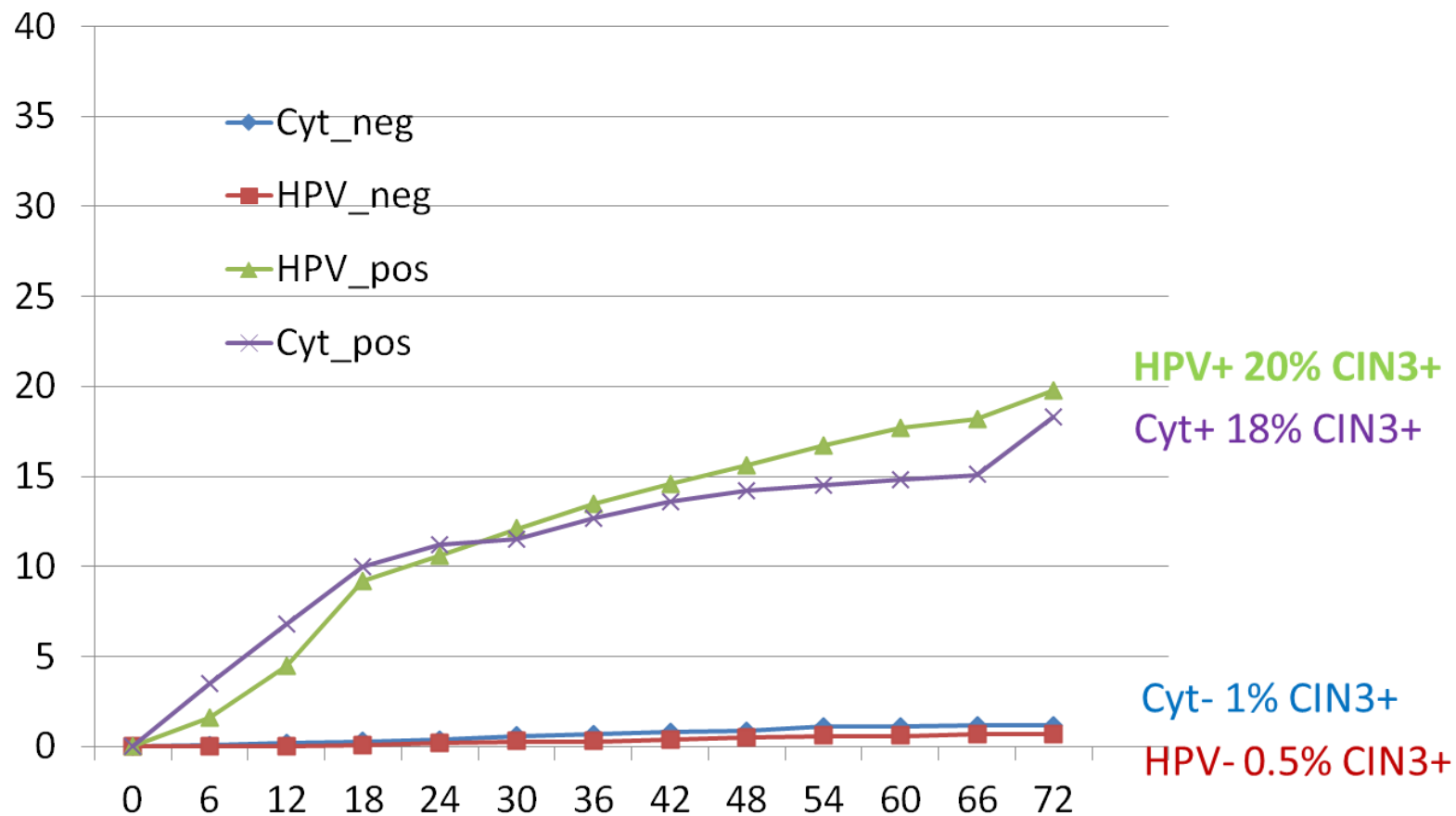


Castle PE, Glass AG, Rush BB, Scott DR, Wentzensen N, Gage JC, Buckland J, Rydzak G, Lorincz AT, Wacholder S. Clinical human papillomavirus detection forecasts cervical cancer risk in women over 18 years of follow-up. *J Clin Oncol*. 2012 Sep 1;30(25):3044-50. doi: 10.1200/JCO.2011.38.8389.

# HPV mRNA testing by PreTect technology

- The E6/E7 mRNA tests have higher specificity for high-grade cervical disease and cancer and could serve as a **better risk evaluation factor**, reducing colposcopy referral and over-treatment
- A 5-type HPV mRNA E6/E7 test holds a lower sensitivity for detecting CIN2+ than a 14-type HPV DNA test, however it is probable that it identifies most lesions that are destined to progress to cancer

# HPV mRNA E6/E7 versus Cytology



Follow-Up Duration (months)

**HPV mRNA test: PreTect HPV-Proofer (5 types)**

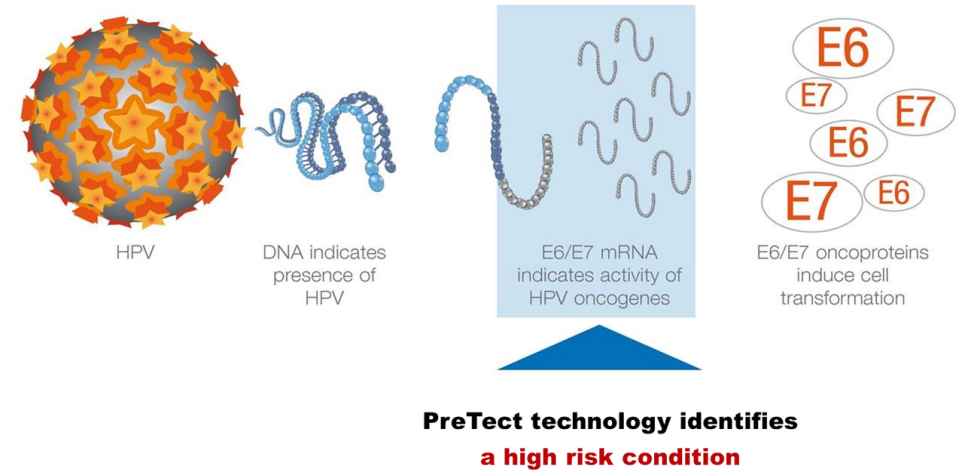
\*Sørbye et al 2016: Study population: 12,616 women 21-65 yrs.



Sensitivity in women with cervical cancer

	N	HPV MRNA	HPV DNA
Lie 2005	20	100%	90% (HC2)
Moekel 2007	35	97%	94% (HC2)
Kraus 2006	204	89%	92% (GP5+/6+)
Basu 2009	273	83%	83% (MY09/11)
Hovland 2010	98	64%	62% (GP5+/6+)
Rad 2017	167	92%	92% (GP5+/6+)
Dabeski 2019	24	96%	88% (GP5+/6+)
<b>Total</b>	<b>821</b>	<b>86%</b>	<b>86%</b>

- HPV is a common virus and 70-80% of all women are infected during lifetime
- A positive HPV-DNA test result provides little actionable information
- The real cause of cervical cancer is not the HPV infection per se, but over-expression of E6 and E7 oncoproteins
- The E6/E7 mRNA test has higher specificity for high-grade cervical disease and cancer and will serve as a better risk stratification, reducing colposcopy referral and over-treatment



# Conclusions

An aerial night view of Tromsø, Norway, showing the city lights reflecting on the water and the Aurora Borealis in the dark sky. The city is illuminated with warm yellow and orange lights, while the surrounding landscape is dark with some snow-covered mountains in the background. The Aurora Borealis is a vibrant green, appearing as a large, ethereal shape in the sky.

*Tromsø*  
the Gateway to the Arctic

**MUCHAS GRACIAS!**