EUROGIN 2023, Bilbao – Interesting things to know about

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with contributions from
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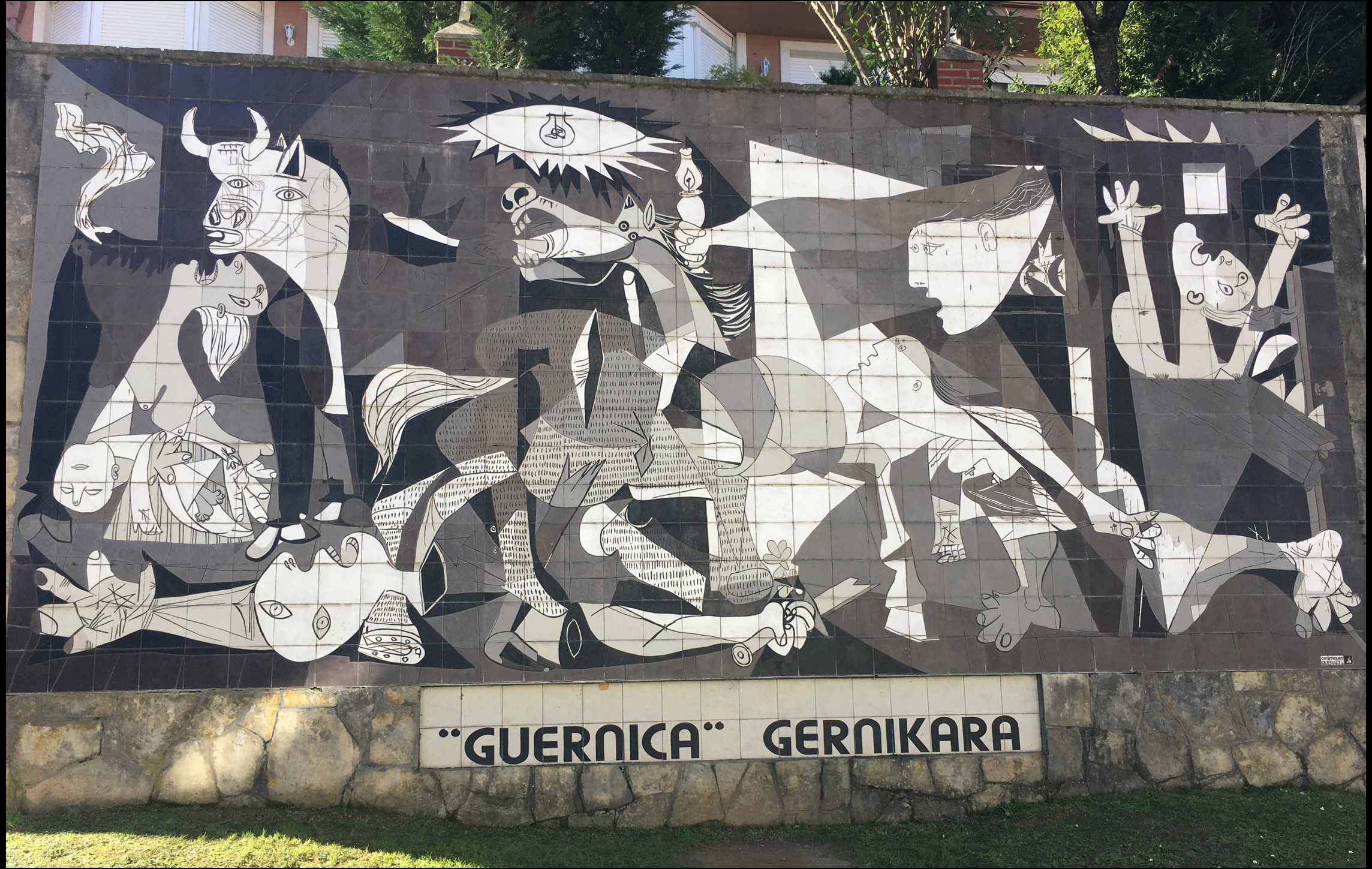
Outline

Risk stratification

Role of males

Cervical cancer elimination

Test validation


"GUERNICA" GERNIKARA

Risk stratification

- HPV presence/absence/genotype and persistence
- Other views of what HPV is doing:
    - p16/Ki67 (CINTec+)
    - Cytology
    - Methylation – host and/or viral
    - Protein/RNA expression
- Use of information
    - Screening
    - Disease management
        - triage
        - treatment/post treatment monitoring

HPV presence/absence/ genotype and persistence

- HPV negative cervical, vulval, anal and oropharyngeal cancers do worse
  - 7% cervical cancers; 11% anal cancers HPV negative
  - Integration of HPV into host genome ⇒ worse outcome
  - Higher viral load may be associated with better survival
- HPV genotype indicates risk of disease but not presence – persistence increases likelihood of disease
  - HPV 16/18 at primary screening no better than cytology triage and follow up over screening round
  - Persistence of genotype over 12 months predicts recurrence of high grade disease

Other views of what HPV is doing

Depends upon how good your cytology is …

p16/Ki67 staining

- upstream marker compared to cytology so useful if cytology negative

Cytology (ASCUS+)

- better than genotyping for all types except HPV16 at identifying risk
- needs clinician–taken samples

Methlyation

- host cell/viral/both – Netherlands uses host; both in UK(S5)
- developed using referral populations; need to validate on screening populations before general use

Proteins/RNA/circulating HPV DNA

Use of information

Primary screening

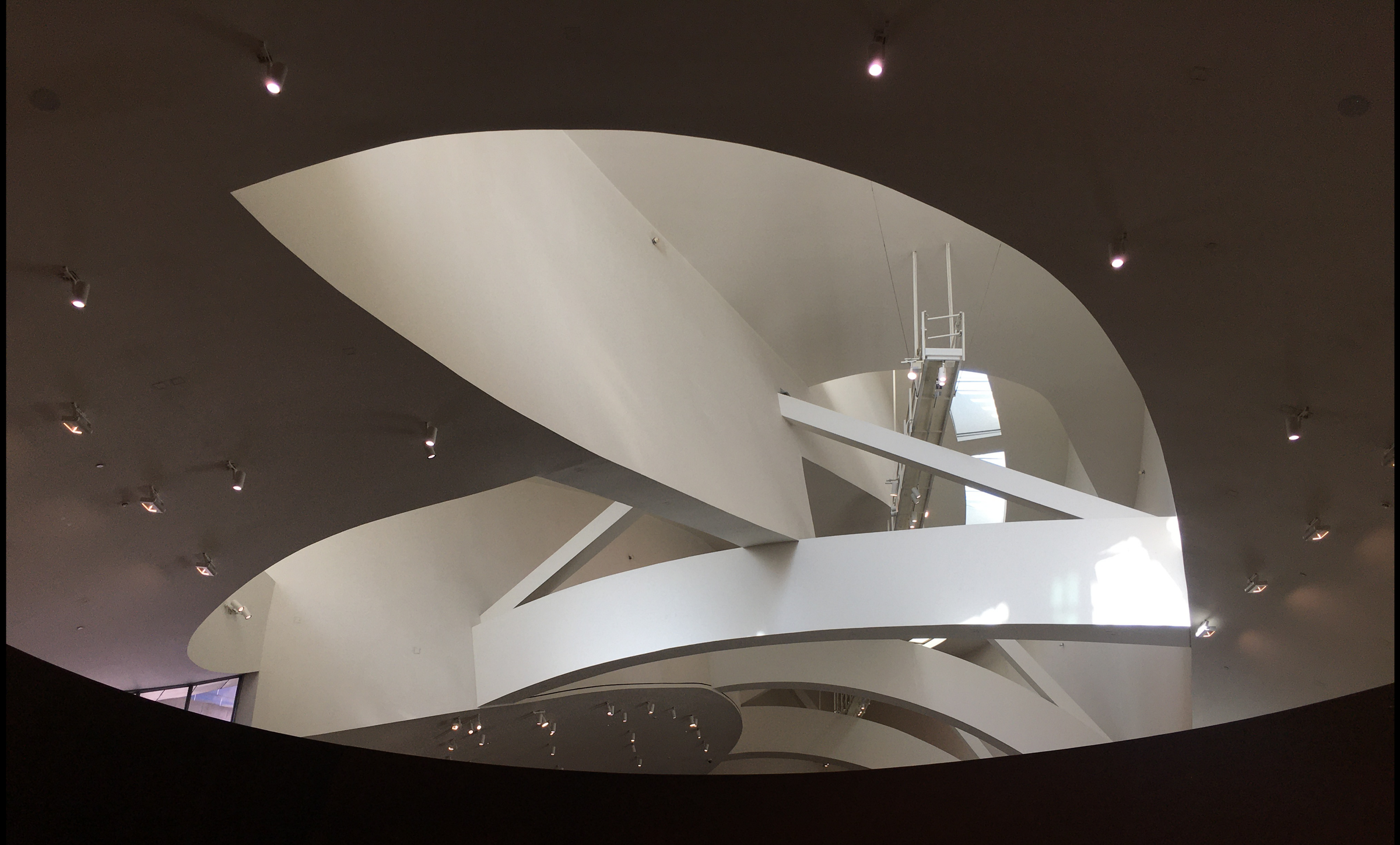
- Genotyping the referring sample may help subsequent monitoring

Triage

- Methylation better PPV for HG disease than 16/18
- Cytology (if good enough) still good as first-line triage
- CINTec+ better than negative cytology
- Low methylation may predict potential for regression of disease associated with low grade cytology
- Methylation probably not ready for widespread use on its own

Treatment/post treatment monitoring

- Type persistence and also circulating HPV DNA may predict relapse



Rôle of males – transmission

Transmission of HPV

- HITCH and CATCH studies (E. Franco, Montreal)
- Women typically 3–5 yr younger than male partner at sexual debut
- Women acquire HPV within a few months of sexual debut
- Concordance between HPV types between partners
- Women clear HPV quicker than males (seroconversion)
- Prevalence of HPV remains high in males for longer than in women
- HPV 16 less common in males than in women
- Bisexual men form a link between MSM and women
- MSW may also be MSM but don’t admit it

Rôle of males – vaccination

Why vaccinate males?

- Cancers in males – anal, oropharyngeal
- MSM
- Improves herd protection/CaCx elimination progress
- Not cost-effective in HIC with high uptake rates
- Not ethical in a global context

Does it work?

- Vaccination at ≤18 yr gives good antibody levels
- Antibody long lasting
- Equivalent protection to females at 2 doses;1 dose like natural infection
- Works in HIV+ MSM/MSW

Cervical cancer elimination

- Cervical screening
  - Improve uptake – communication; self sampling
  - How often and how?
  - Validation of tests
- Treatment of HG disease
  - Prediction of who needs treatment
  - Who is cured and who might relapse/recur
- HPV immunisation
  - Can HPV 16 be eradicated?

Cervical cancer elimination – role of screening

"With high coverage, screening intensity is the best option"

How to improve coverage

- identify areas of poor coverage – age; ethnicity; deprivation; immigrants
- improve communication – text messaging
- make it easier to attend – 'women's health clinics'; offer appointment
- make it a better experience – self-sampling

Cervical cancer elimination – disease management

Who needs treatment

Triage strategies – how to assess cytology negative cases

Improving and monitoring treatment

Post colposcopy vaccination – SPERANZA trial

Test of cure – benefit of cytology disputed

– extended genotyping

– genotype persistence

– viral load

Relapse of invasive disease – circulating HPV DNA (ddpcr)

Cervical cancer elimination – role of vaccination

HPV ‘even faster’

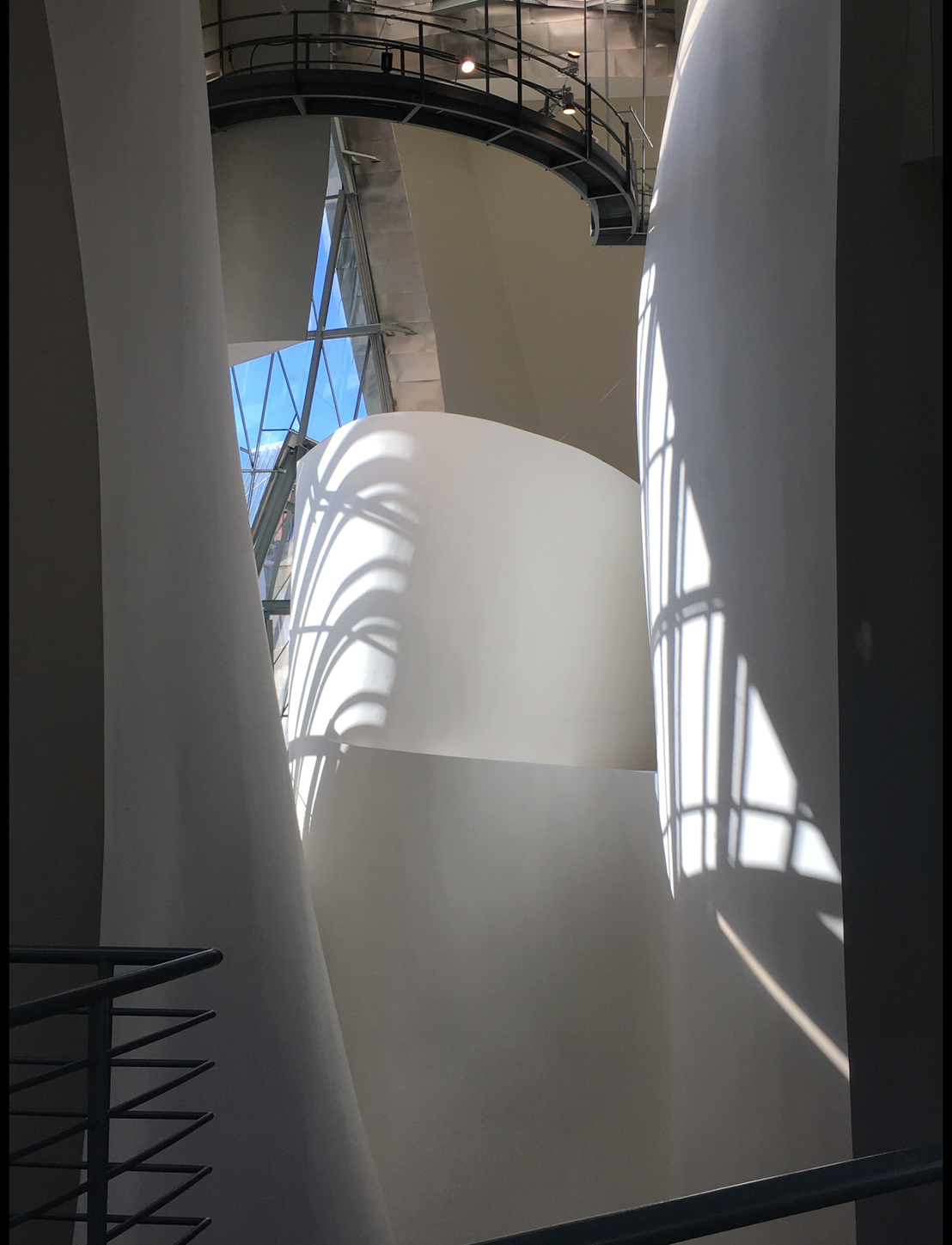
- R number for HPV varies with: HPV type (16 ~ 3.3; 18 ~ 1.8)
  age (≥25: 1.3; ≥30: 1.0; ≥35: 0.4)
- Push for screening and vaccination in women aet ≤30 yrs
- HPV prevalence in unscreened 27% (mostly non 16/18)

Gender neutral vaccination and HPV16 elimination

- 50% uptake in girls – no herd protection or HPV type elimination
- 40% girls + 20% boys – herd protection for HPV16
- At least 75% uptake of girls only to get elimination of HPV16

Cervical cancer elimination – role of vaccination *continued*

- Vaccine choice
  - Cervarix produces sustained antibody against 16/18/31/33/45
  - ASO4 adjuvant produces better and longer lasting immunity
  - Serology correlates with vaccine efficacy for Cervarix
  - Sustained VE for G4 despite waning antibody – why?
- Reservoir populations
  - Unvaccinated individuals sustain HPV in girls-only programmes so transmission continues – deprivation; BAME; males



Cervical cancer elimination – validation of tests

- Uses for tests
  - Primary screening
  - Triage
  - Test of cure
  - Self-sampling

- Primary Screening
  - Meijer criteria – screening populations
  - VALGENT protocol – disease-enriched panels
- Triage
  - ASCUS+/HPV+ ≠ HPV+/ASCUS+
- Test of Cure
  - STOCS-H and ATOC studies
- Self-sampling
  - VALHUDES protocol

Cervical cancer elimination – validation of tests for TOC

CIN3+	ATOC performance (%; 95% CI)				Relative performance (%; 95% CI)			
	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
Real Time	97.1 *85.1-99.9*	70.7 *63.7-77.1*	38.2 *28.3-49.2*	99.3 *95.3-100*	1	1	1	1
Aptima	100 *91.8-100*	73.8 *66.7-79.9*	42.2 *31.6-53.5*	100 *96.6-100*	1.03 *0.97-1.09*	1.04 *0.92-1.18*	1.10 *0.77-1.59*	1.01 *0.99-1.02*

CIN3+	Clinical performance (%; 95% CI)				Relative performance (%; 95% CI)			
24/12 fu	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
HC2/ Real Time	98.8 *97.4-99.5*	76.5 *76.1-76.9*	6.1 *5.7-6.7*	99.9 *99.9-100*	1	1	1	1
Aptima	94.6 *85.1-98.9*	77.8 *75.6-79.9*	14.0 *10.7-17.9*	99.7 *99.2-99.9*	0.98 *0.91-1.03*	1.01 *0.98-1.04*	1.33 *1.03-1.71*	1 *0.99-1.01*

- Aptima showing equivalent sensitivity, specificity and NPV to previous TOC testing
- PPV for Aptima better than previous TOC testing
- ATOC used a VALGENT-like protocol with disease enriched panels
- CIN3 rates declining in screening population

Cervical cancer elimination – validation of tests

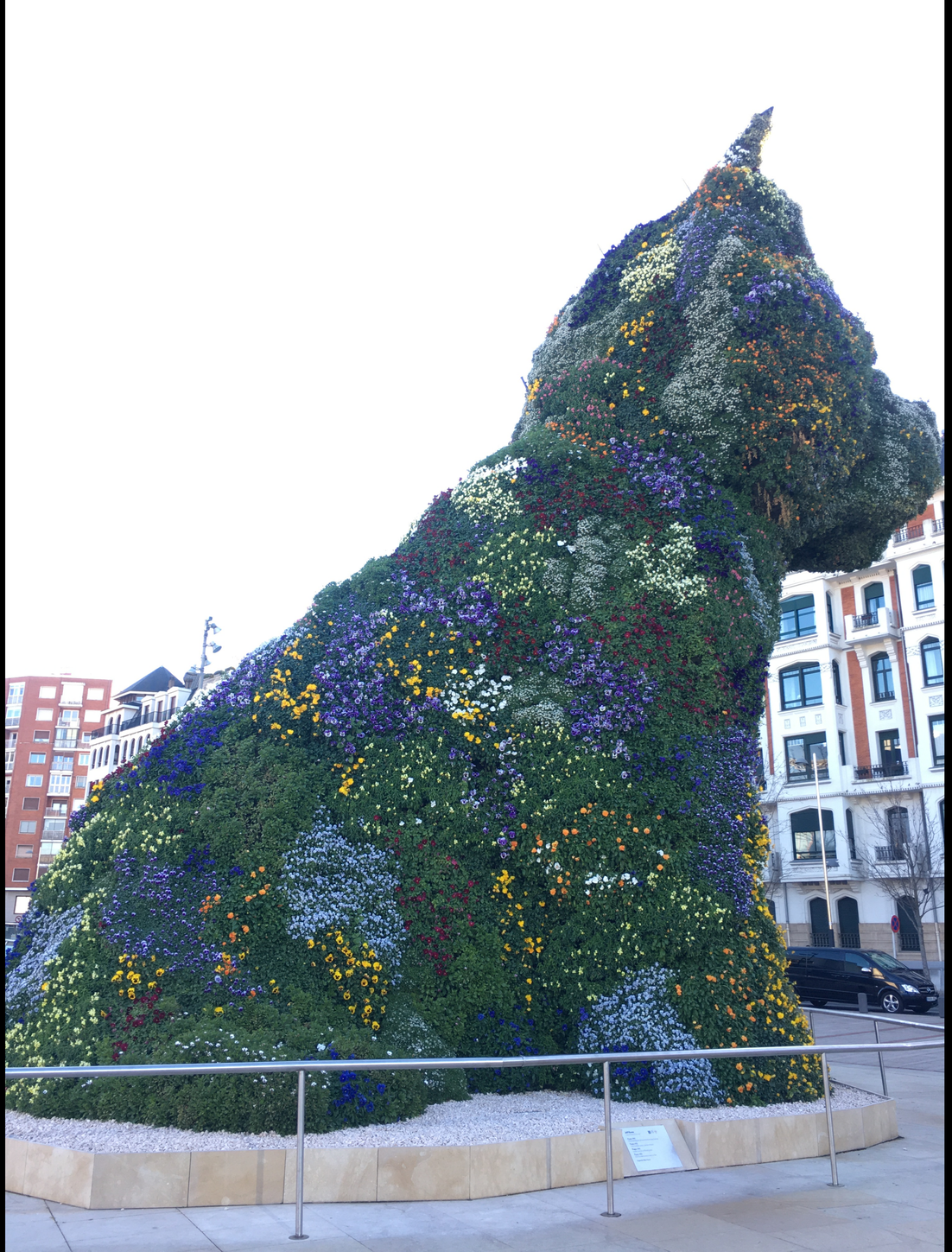
Summary: likely effect on the accuracy of HPV testing

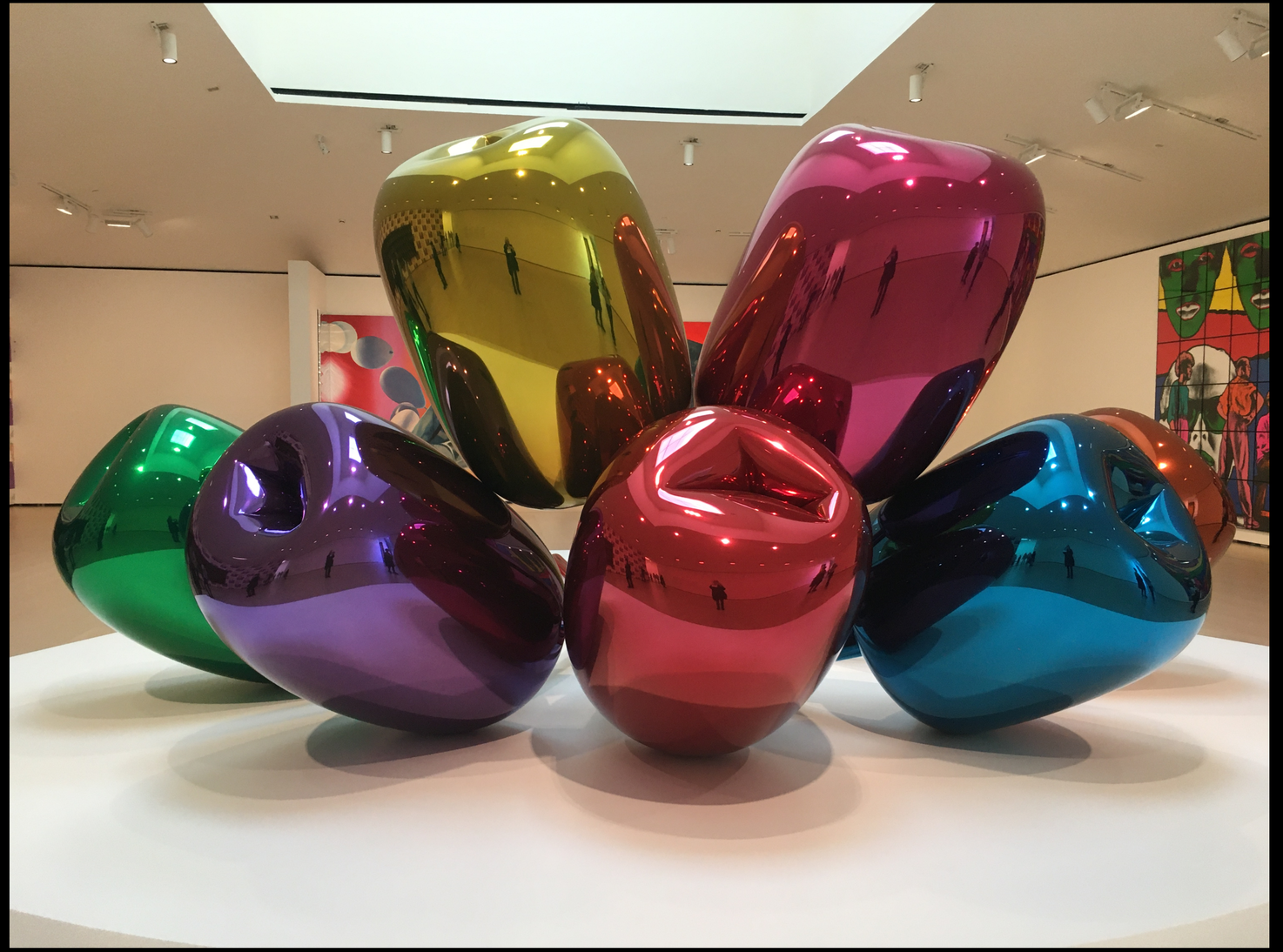
	Sensitivity	Specificity	PPV for CIN2+
Cross-protection	↓	↓	↓
Analytical unmasking	↑ (analytical)	↔? (analytical)	↑? (analytical)
Clinical unmasking (misattr.)	↑	↑	↑
Clinical unmasking (intact TZ #1)	↑	↑?	↑
Clinical unmasking (intact TZ #2)	↑?	↓	↓

- Which effect is dominant?
- What will be the overall effect?
- Uncertainty for programmes

Table courtesy of Matejka Rebolj, Kings College London.

- Screening tests perform less well as prevalence falls
- HPV immunisation shown to affect cytology performance
- Vaccines vary in their spectrum of protection
- Removal of HPV16 may reveal co-infecting types





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