Riflessioni sulle raccomandazioni per la genotipizzazione in ambito europeo

Reflections about the recommendations about genotyping in Europe

Paolo Giorgi Rossi e Marco Zappa

Marco Zappa
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

Paolo Giorgi Rossi

dichiara

Che, come PI di uno studio indipendente finanziato dal Ministero della Salute, ha condotto trattative con Roche, Hologic e Becton Dickinson per ottenere reagenti a prezzo ridotto o gratis

Comparing the recommendations

Italy

- Screening for vaccinated: tailored
- 3-groups extended genotyping
- Equal risk equal management approach
- Other risk factors
  - Vaccination
- Shorter intervals

Sweden

- Screening for vaccinated: by age/cohort
- 3-groups extended genotyping
- Test result-based approach
- Other risk factors
  - Age
- Longer intervals

3-group genotyping

Italy

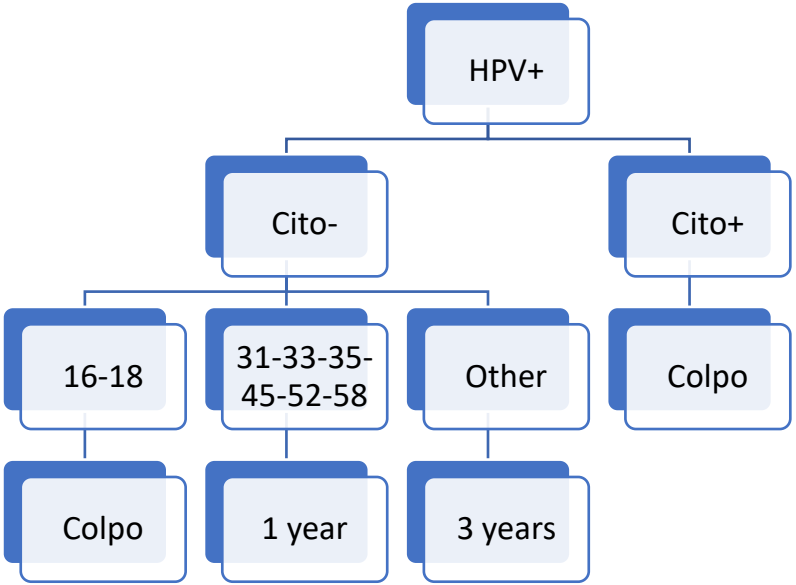
- **16-18**
- **31-33-35-45-52-58**
- **39-51-56-59-66-68**

Sweden

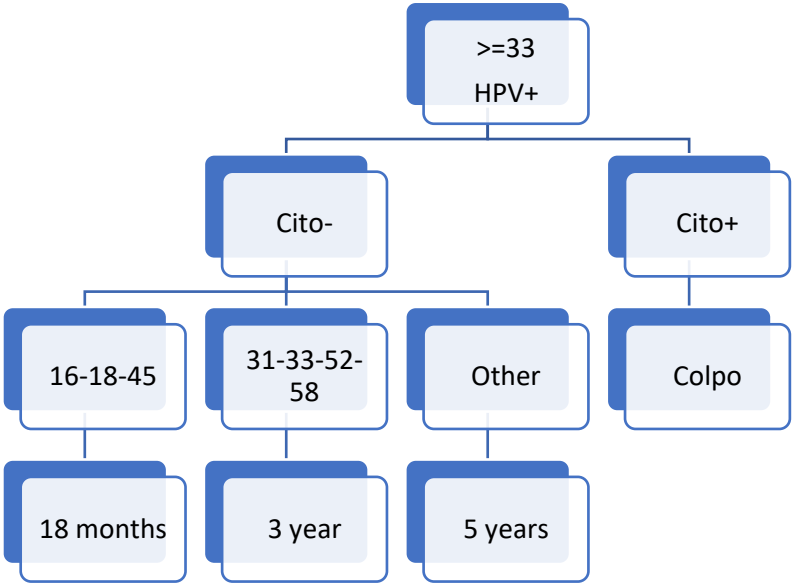
- **16-18-45**
- **31-33-52-58**
- **35-39-51-56-59-66-68**

Intervals for HPV+ women

Italy



Sweden



Approach for vaccinted women

Italy

- Women vaccinated <15 years with 2+ doses start screening at 30 with HPV test
- Women not-vaccinated or vaccinated later than 15 yo start screening at 25 with Pap (then shift to HPV at 30/35)

Sweden

- Women from cohorts with high coverage start at the same age but
- if HPV-positive for **35-39-51-56-59-66-68** are rescreened after 5.
- If positive for 16-18-45-31-33-52-58 undergo cytology.
- If negative for cytology, according to genotype:
  - 16-18-45 18 months
  - 31-33-52-58 5 years

The European Commission Initiative on Cervical Cancer

Image source: IARC Twitter (@IARCWHO), 1.12.2023, https://twitter.com/IARCWHO/status/1723985153251307885

International Agency for Research on Cancer

World Health Organization

European Commission

The EC-CvC initiative

- Promoted by the European Commission
- Coordinated by IARC
- Adopt GRADE methodology
- Will use a risk-based approach

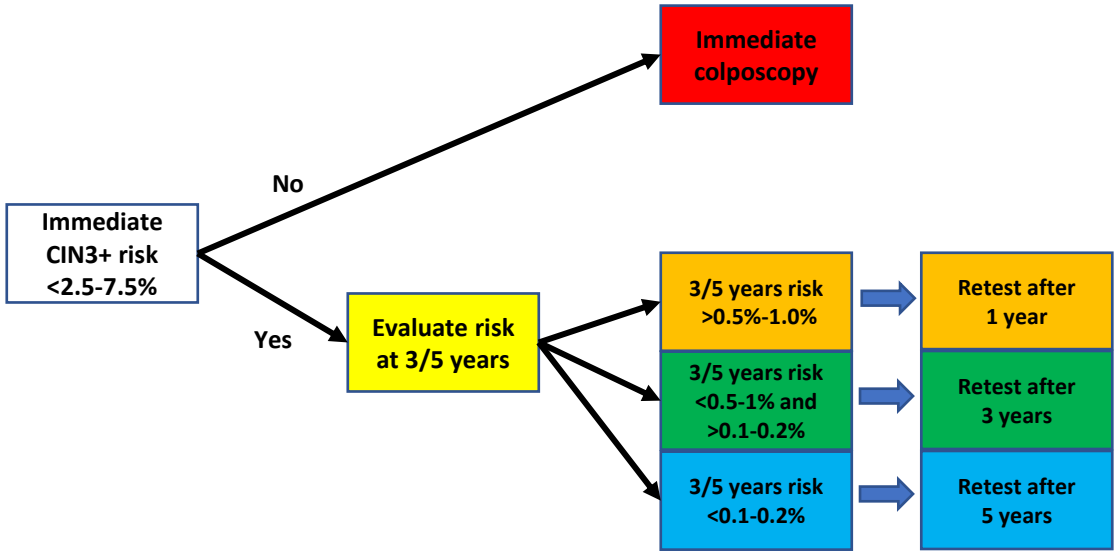
How to measure the risk-reduction in vaccinated women.

- Individual-level assessment:
  - Not easy to implement in many countries
- Cohort approach
  - Assessing the vaccine coverage
    - Indirect, needs assumption on herd immunity
  - Assessing HPV prevalence:
    - Direct measure of risk in the population, but it needs type specific prevalence!

Extended genotyping in screening is the only solution to measure type-specific HPV prevalence and applying a cohort based approach.

Risk-stratification: the limits of using CIN3+ cumulative incidence as surrogate of cancer risk

- When risk stratification is based on genotyping the assumption that CIN3+ cumulative incidence reflects the risk of cancer has serious limits:
  - A CIN3 linked to HPV 39 does not have the same risk of progress to cancer in the next years of CIN3 linked to HPV 16!



In Italian GGLL, these three risk levels are relevant for triage

	Any HPV
Cytology high-grade	Colposcopy (PPV 22%)
Cytology low-grade	Colposcopy (PPV 3%)
NILM	1-year (PPV 1%)

With cytology triage, CIN3 from the three groups on average have the same risk of progression to cancer

Prevalence of CIN3+ (assessd within 24 months)

	HPV 16-18	HPV 31-33-35-45-52-58	HPV 39-51-56-59-66-68
Cytology high-grade	Colposcopy (PPV 36%)	Colposcopy (PPV 19%)	Colposcopy (PPV 22%)
Cytology low-grade	Colposcopy (PPV 5,5%)	Colposcopy (PPV 3,1%)	1 year referral (PPV 1,1%)
NILM	Colposcopy (PPV 3,4%)	1 year referral (PPV 1,5%)	3 year referral (risk 0,4%)

1 Cancer out of 3 CIN3 | 1 out of 10 | 1 out of 100

Prevalence of CIN3+ (assessed within 24 months)

Comparing two triage strategies

Triage strategy a	Triage strategy b
10%	20%
30%	50%
60%	30%

Easy to see that «a» is better than «b»!

Comparing two triage strategies

Triage strategy a	Triage strategy b
15%	20%
40%	30%
45%	50%

Here is more difficult to decide whether is better a or b.
We should know what the yellow implies:
How many colposcopies?
How many follow up episodes?
It depends on the clearance rate.
That depends on the genotype!

Comparing two triage strategies

Triage strategy a	Triage strategy b
10%	10%
30%	40%
60% (rischio a 3aa 0,5%)	50% (rischio a 3aa 0,2%)

The threshold for referring at three years is very cautious, nevertheless the risk profile in strategy “b” is apparently better than in strategy “a” …
Again it depends on the type mix included in the green boxes: if the two strategies use genotyping differently the values of CIN3+ risk re not comparable because they do not underly the same risk of cancer

The limits of using CIN3+ cumulative incidence as surrogate of cancer risk: vaccination

- The link between CIN3 cumulative incidence and risk of cancer is not the same in vaccinated and non-vaccinated women/populations:
  - Post- and pre-vaccination HPV+ populations have a different type-mix, thus thy have different risks of cancer even if they have similar CIN3.
  - On the other hand, in sub-population with similar type mix, i.e. when using extended genotyping, the effect of vaccination has little influence on risk, given that the infection is present.

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NILM	Colposcopy (PPV 3,4%)	1 year referral (PPV 1,5%)	3 year referral (risk 0,4%)

Does not change in vaccinated women

Partially changes in vaccinated women

Should not change in vaccinated women

Prevalence of CIN3+ (assessd within 24 months)

	Any HPV
Cytology high-grade	Colposcopy (PPV 22%)
Cytology low-grade	Colposcopy (PPV 3%)
NILM	Colposcopy (PPV 1%)

Completely dependent on the HPV type mix.
It changes in vaccinated women!

Prevalence of CIN3+ (assessed within 24 months)

Take home message

- Genotyping allows a very precise risk stratification of HPV+ women
- Italian and Swedish guidelines are both deintensifying screening
  - The main differences are due to individual vaccination assessment and cohort/age approach
  - Italian GGLL recommend shorter intervals for HPV+ women
- Genotyping is functional to afford screening in vaccinated women:
  - For monitoring and decision making
  - For deintensification of protocols with a biomarker that is almost independent from vaccine status

The aim of risk-stratified screening is to achieve a better balance between harms and benefit

Risk stratified screening **increases** the intensity of screening in people with **higher risk** and **reduces** the intensity of screening in people with **lower risk**. We must consider that the majority of people participating in screening will never have the target cancer but many will suffer some of the undesirable effects of screening.

The point of view of the **community**

With a risk stratified screening a more cost effectiveness result can be obtained:

➔ With the same amount of resources a higher number of outcomes can be obtained, or the same number of outcomes can be obtained with lower amount of resources.

	Standard screening	Risk-based screening	Difference in Cancer prevented
High risk	70 treatments to prevent 10 cancers (NNT 7)	140 treatments to prevent 14 cancers (NNT 10)	+4
Average risk	120 treatments to prevent 12 cancers (NNT 10)	120 treatments to prevent 12 cancers (NNT 10)	0
Low risk	140 treatments to prevent 7 cancers (NNT 20)	50 treatments to prevent 5 cancers (NNT 10)	-2

330 treatments to prevent 19 cancers

310 treatments to prevent 21 cancers

The point of view of the individual

If a woman is stratified in a **Low Risk Group** she will experience :

- a lower number of tests;
- a lower lifetime probability of a false positive result;
- lower side effects of assessment ;
- But it is possible that **she will feel less protected .**

A woman HPV (low oncogenity types) + / Cyto – will repeat the test after 3 years (now is after 1 year)

- Large spontaneous activity

- The side effects of assesment are relatively low

we are able to identify very different levels of risk

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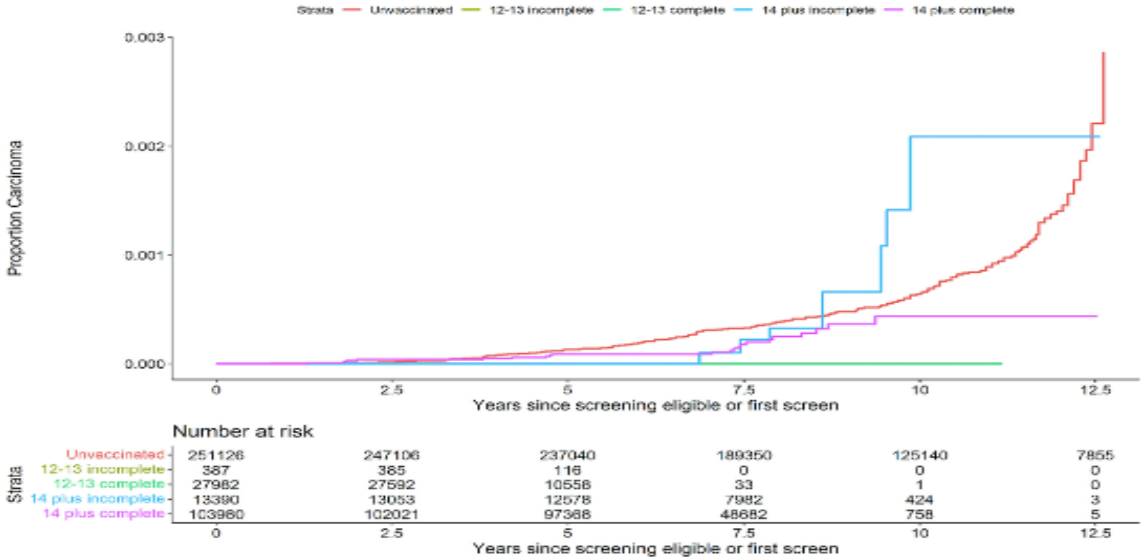
due to vaccination the risk of cervical cancer is decreasing although it is not yet perceived



ig. 6. Kaplan-Meier curve of diagnosis of cervical carcinoma as time in the screening program increases by vaccination status and age at vaccination.[3] Vaccination atus: Unvaccinated (no doses given), Incomplete (1 dose or 2 doses 1 month apart), and Complete (2 doses at least 5 months apart or 3 doses). Note that although

Cameron et al, :Assessing real world vaccine effectiveness: A review of Scotland's approach. Vaccine 2024