CERVICAL CANCER SCREENING WITH HPV DNA: UP TO DATE INFO FROM EUROPE

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Hacettepe University, Gyn Oncol Division
ESGO Vice President
No, nothing to disclose

Yes, please specify:

<table>
<thead>
<tr>
<th>Company/Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/Patent</th>
<th>Stock Options</th>
<th>Ownership/Equity Position</th>
<th>Employee</th>
<th>Other (please specify)</th>
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</table>
Cervical Cancer Globally

✓ Half Million New Cases
✓ 50% Mortality
✓ >90-99.7% HPV Related
✓ Preventable Cancer
  ✓ HPV Vaccination, Smoking Cessation
✓ Early Detection is Possible
  ✓ VIA-VILI / Smear / HPV / Combination / Others
  ✓ WHO
✓ Eradicable Cancer
Cervical Cancer Last Century

✓ Cytology based screening programs have reduced more than 75% of incidence and mortality from cervical cancer in the last 50 years.

✓ Especially in developed countries.

✓ However, only 12 countries have succeeded in EUROPE (2017).

✓ And still cervical cancer mortality does not decrease any more even in most developed countries.
Current Status

Cancer Screening in the European Union (2017)

Report on the implementation of the Council Recommendation on cancer screening

Second Report on Cancer Screening in EU

- **Main collaborating institutions**
  - International Agency for Research on Cancer, Lyon, France (coordination)
  - CPO Piemonte, University Hospital “Città della Salute e della Scienza” CPO, Turin, Italy
  - Finnish Cancer Registry, Mass Screening Registry, Helsinki, Finland

- **Over 80 Data providers from all 28 EU Member States**

Data Provider’s Workshop (22 Member States Participating) – 16-17 Feb, 2016; IARC
# Cervical Screening Programs in EU

<table>
<thead>
<tr>
<th>Type</th>
<th>1st Report 2008</th>
<th>2nd Report 2016</th>
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<tbody>
<tr>
<td>Population based program</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>• Rollout complete</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>• Rollout ongoing</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>• Pilot</td>
<td>1</td>
<td>1</td>
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<tr>
<td>• Planning</td>
<td>2</td>
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<tr>
<td>Non-population based program</td>
<td>12</td>
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</table>
Cervical Cancer Screening Programs in the EU 2016
## Target Ages and Screening Intervals of EU

<table>
<thead>
<tr>
<th>Country</th>
<th>Pop based program</th>
<th>Target age</th>
<th>Screening interval</th>
<th>HPV Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>✗</td>
<td>18 &amp; above</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>✓</td>
<td>25 – 64</td>
<td>3</td>
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<tr>
<td>Bulgaria</td>
<td>✗</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Croatia</td>
<td>✓</td>
<td>25 - 64</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cyprus</td>
<td>✗</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Czech Rep</td>
<td>✓</td>
<td>15 &amp; above</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>✓</td>
<td>23 - 65</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Estonia</td>
<td>✓</td>
<td>30 - 59</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>✓</td>
<td>30 - 34</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>✓</td>
<td>25 - 64</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>✓</td>
<td>20 &amp; above</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>✗</td>
<td>Sexual onset</td>
<td>NA</td>
<td></td>
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<tr>
<td>Hungary</td>
<td>✓</td>
<td>25 - 65</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>✓</td>
<td>25 - 60</td>
<td>3 (25-44); 5 (45-60)</td>
<td>60 – 65 (5 yr int)</td>
</tr>
<tr>
<td>Italy</td>
<td>✓</td>
<td>25 - 64</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Latvia</td>
<td>✓</td>
<td>25 – 69</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Lithuania</td>
<td>✓</td>
<td>25 - 59</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Luxembourg</td>
<td>✗</td>
<td>18 &amp; above</td>
<td>1</td>
<td></td>
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<tr>
<td>Malta</td>
<td>✓</td>
<td>25 – 64</td>
<td>3</td>
<td>30-64 (co-test)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>✓</td>
<td>25 - 64</td>
<td>3</td>
<td>30-59 (co-test)</td>
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<tr>
<td>Poland</td>
<td>✓</td>
<td>25 - 59</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td>✓</td>
<td>20 - 59</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Romania</td>
<td>✓</td>
<td>25 – 64</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Slovak Rep</td>
<td>✓</td>
<td>23 - 64</td>
<td>Yrly x 2; then 3 yrly</td>
<td></td>
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<tr>
<td>Slovenia</td>
<td>✓</td>
<td>20 - 64</td>
<td>Yrly x 2; then 3 yrly</td>
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<tr>
<td>Spain</td>
<td>✓</td>
<td>25 - 64</td>
<td>3</td>
<td>Unpublished data; Not to be quoted</td>
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<tr>
<td>Sweden</td>
<td>✓</td>
<td>23 - 60</td>
<td>3 (23-50); 5 (51-60)</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>✓</td>
<td>25-64</td>
<td>3 (25-59); 5 (60-64)</td>
<td></td>
</tr>
</tbody>
</table>
Cytology Based Screening: International Problems

✓ Scientific Problems
  • A single Pap-Test has a very low sensitivity for CIN2+ lesions
  • Pap-Test has a high false negative rate
  • Reproducibility of Pap-Test is low
  • Pap-Test is less effective in detecting adenocarcinoma of cervix

✓ Organisational Problems
  • It is a very difficult and complex service to provide.
HPV DNA As a New SCREENING TOOL
20 Years Research Summary: Sensitivity and Specificity

- Low Specificity may cause unnecessary colposcopies
  - Can Be Compensated With Additional Tirage Tests and age for Screening >30 years
  - HPV Genotyping, Reflex Cytology, Cytology Stainings with p16 with or without Ki-67, Methylation Profiles

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
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</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>53%</td>
<td>97%</td>
</tr>
<tr>
<td>HPV test</td>
<td>96%</td>
<td>92%</td>
</tr>
</tbody>
</table>

**HPV DNA As a New SCREENING TOOL**

20 Years Research Summary: Co-Test or Alone?

After 2012, Guidelines Has Changed

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Target</th>
<th>Relative Sensitivity</th>
<th>Relative Specificity</th>
<th>Trial Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyto + HPV vs. Only HPV</td>
<td>CIN2+</td>
<td>1,05</td>
<td>0,95</td>
<td>10</td>
</tr>
<tr>
<td>Cyto + HPV vs. Only HPV</td>
<td>CIN3+</td>
<td>1,02</td>
<td>0,93</td>
<td>6</td>
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</tbody>
</table>

HPV DNA As a New SCREENING TOOL
20 Years Research Summary: Negative Predictivity

Articles

Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials

Guglielmo Ronco, Joakim Dillner, K-Miriam Eidstrøm, Sara Tunesi, Peter JF Snijders, Marc Arbyn, Henrik Kerchner, Ninoe Seppanen, Clare Gilham, Paolo Giorgi Rossi, Johannes Berkhof, Julian Peto, Chris JLM Midler, and the International HPV screening working group*

✓ Cumulative Cervical Cancer Incidences for negative initial tests:

Negative cytology;
Negative HPV test;

3,5 years 5,5 years
15.4 / 10⁵ 36.0 / 10⁵
4.6 / 10⁵ 8.7 / 10⁵

Cumulative incidence rate (per 10⁵)
European Guidelines and All International Guidelines Has Changed

✓ EU 2008 Guidelines
  ▪ More data is needed to recommend HPV DNA for primary screening

✓ EU 2012 Guidelines Supplement
  ▪ HPV DNA can be used alone for primary cervical carcinoma screening

✓ FDA, EFC, ASCCP, SGO
HPV DNA in Europe

✓ Turkey
✓ Netherlands
✓ Italy: Currently 8 regions, all regions by 2018
✓ Denmark, Poland, Malta, Switzerland, Norway
✓ 2017/2018: England, Denmark, Germany ....
On the Pipeline for HPV DNA Screening
Point of Care / Convenience Testing

✓ 9 Reguler Kits
✓ HPV DNA
  - Cepheid-X-pert
  - Qiagen Care HPV
  - Urine-Trovagen
✓ Oncoproteins-E6/E7
  - Arbovita
  - Oncohealth
✓ Self HPV Sampling
  - Similar accuracy to clinician collected samples with validated PCR based kits
HPV Faster

Current cervical cancer preventive strategies (simplified) and proposed HPV FASTER initiative

- Cytology x 3 yrs.
- Cytology (x3 to age 25/30) & HPV test x 5/10 yrs.
- HPV tests x 2/3 lifetime

Routine and Catch-up vaccination: (x2 or x3, based on age)
Cytology screening: ( )
HPV screening ( )
Male vaccination

Exact age limits to be defined
Screening in Post-Vaccination Era

✓ Some form of cervical screening will be needed for the foreseeable future
✓ Lower prevalence of CIN2+ due to lack of HPV vaccine type induced lesions
✓ Decreased sensitivity for cytology
  ▪ Rare abnormalities, lack of experience and lack of concentration
✓ Decreased PPV for cytology
  ▪ False positives will not change but true positives will decrease
✓ Objective, automated methods of HPV screening will be more important for low prevalence setting
✓ Cost effectiveness of screening will decrease
  ▪ Further benefits are likely to accrue by combining HPV Vaccination in older women with HPV Screening-HPV Faster
  ▪ This should be compensated with longer screening intervals
CASE STUDY with HPV DNA SCREENING

TURKEY
Why HPV For Turkey?

✓ For Screening Program Directors
  ▪ Higher sensitivity
  ▪ High Negative Predictive Value and Longer Screening Intervals
  ▪ Low HPV positivity (low prevalence)

✓ For Academicians
  ▪ Manpower advantage
  ▪ Central quality control and automatisation

✓ For Ladies
  ▪ Shortening the time to final diagnosis
  ▪ Self-testing ability for future a new test for ladies attention
Results: Population Based Cancer Screening

![Graph showing the increase in cancer screening population over years.]
A total of 2,800,000 were screened by HPV test.

Approximately 24,000 cancer cases were prevented (Except ASC-US)

HPV Mapping of Turkey
Challenges

- Resistance of cyto-pathology experts
- HPV is a sexually transmitted disease
- Resistance of GP for screening
- GP and nurses were not well trained for HPV
- HPV vaccination was not available
- Questions about adult vaccinations
- Colposcopy trainings quality
Thank you for your attention