The Development and Evaluation of a New Community Based Model for Cervical Cancer Screening Based on Self-Sampling

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Preventive Oncology International, Inc.
www.poiinc.org
"I have received support in kind (reagents and testing) and funds for direct support and research, under the auspices of Preventive Oncology International Inc., from Hologic Inc., Qiagen, Gen-Probe, Merck Inc., BGI Shenzhen, and GE Healthcare."

Jerome L Belinson MD
“Please put on your public health hats, it may not be your focus but it is actually a more stringent test for screening technologies."
Determinants of Screening Algorithms

Sensitivity and specificity of screening tests

Healthcare infrastructure

- Human resources
- Financial resources

Age cancers develop

Prevalence of disease
The Screening Program Must Be Specific To The Target Population
Distribution of Pathologists in Tanzania

▲ = 1 physician
### Per-capita expenditure on healthcare in USA, Argentina, Peru, China and Tanzania

<table>
<thead>
<tr>
<th></th>
<th>Doctors per 10,000 Population</th>
<th>Health Spending % of GDP</th>
<th>Government % contribution</th>
<th>Total per capital spending on healthcare</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>24.22</td>
<td>17.9</td>
<td>53.1</td>
<td>$8362</td>
</tr>
<tr>
<td>Argentina</td>
<td>31.55</td>
<td>8.1</td>
<td>54.6</td>
<td>$1287</td>
</tr>
<tr>
<td>Peru</td>
<td>9.2</td>
<td>5.1</td>
<td>54.0</td>
<td>$481</td>
</tr>
<tr>
<td>China</td>
<td>14.15</td>
<td>5.1</td>
<td>53.6</td>
<td>$379</td>
</tr>
<tr>
<td>Tanzania</td>
<td>0.08</td>
<td>6.0</td>
<td>67.3</td>
<td>$83</td>
</tr>
</tbody>
</table>

Shanxi Province Cervical Cancer Screening Study
A CROSS-SECTIONAL COMPARATIVE TRIAL OF MULTIPLE TECHNIQUES TO DETECT CERVICAL INTRAEPITHELIAL NEOPLASIA

J. Belinson¹, YL. Qiao², R. Pretorius³, WH. Zhang², P. Elson¹, QJ. Pan², K. Keaton¹, L. Li², C. Biscotti¹, SD Rong², A. Dawson¹, LY. Wu², C. Fischer⁴, AL. Lee², A. Lorincz⁵, L. Yang², D. Zahniser⁶, SD Ren⁷

The Departments of Gynecology, Pathology and Biostatistics from ¹The Cleveland Clinic Foundation Cleveland Ohio and ²The Cancer/Institute Hospital Chinese Academy of Medical Sciences Beijing China. ³Department of Gynecologic Oncology and Pelvic Surgery Kaiser Permanente Fontana California. ⁴Optical Biopsy Tech. LLC. Knoxville, Tennessee. ⁵Digene Corp., Silver Spring, Maryland, ⁶Cytyc Corp., Boxborough, Mass. ⁷Women and Children Clinic, Xiangyuan County, Shanxi Province, China.

Belinson JL Gynecol Oncol 83: 439-44, Nov 2001
Sensitivity and Specificity For ≥ CIN II of Screening Tests in SPOCCS I

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV Self-test</td>
<td>71/86 (83%)¹</td>
<td>86%</td>
</tr>
<tr>
<td>HPV Direct Test</td>
<td>82/84 (98%)²</td>
<td>85%³</td>
</tr>
</tbody>
</table>

¹97.6% vs. 83%, Chi-Square=10.71, p<.005
²98% vs. 94%, Chi-Square=1.3, p=0.25
³85% vs. 78%, Chi-Square=30.9, p<.005
PREVALENCE OF TYPE-SPECIFIC HUMAN PAPILLOMAVIRUS (HPV) IN THE ENDOCERVIX, UPPER VAGINA, LOWER VAGINA, AND PERINEUM; IMPLICATIONS FOR VAGINAL SELF-COLLECTION

Jerome L. Belinson MD, You-Lin Qiao MD PhD, Robert G. Pretorius MD, He Wang MD, Jing Li MD, MPH, Jennifer Smith PhD, Raoul J Burchette, MPH

### Sensitivity for ≥ CIN II of HR-HPV by Hybrid Capture II and HR-HPV by Linear Array for five anogenital sites.

<table>
<thead>
<tr>
<th>Anogenital Site</th>
<th>Sensitivity for CIN 2+ of HR-HPV by HC-II</th>
<th>Sensitivity for CIN 2+ of HR-HPV by Linear Array</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocervix</td>
<td>97.9% (46/47)</td>
<td>100.0% (47/47)</td>
</tr>
<tr>
<td>Upper Vagina</td>
<td>91.5% (43/47)</td>
<td>97.9% (46/47)</td>
</tr>
<tr>
<td>Lower vagina</td>
<td>85.1% (40/47)</td>
<td>95.7% (45/47)</td>
</tr>
<tr>
<td>Perineum</td>
<td>46.8% (22/47)</td>
<td>91.5% (43/47)</td>
</tr>
<tr>
<td>Vaginal self-collection</td>
<td>80.9% (38/47)</td>
<td>95.7% (45/47)</td>
</tr>
</tbody>
</table>
6th Generation POI/NIH Self-Sampler
Improved sensitivity of vaginal self-collection and high-risk human papillomavirus testing

Jerome L Belinson MD, Hui Du MD, Bin Yang MD, PhD, Ruifang Wu MD, Suzanne E Belinson PhD, Xinfeng Qu MD, Robert G Pretorius MD, Xin Yi, Philip E Castle PhD, MPH

Int J Cancer. 2011 May 31
MALDI-TOF and Cervista by Brush

P-Value: .7795

PAUC
Cervista – POI/NIH .0797
Cervista – “Cone” .0769

LEGEND (Test – Brush)
Cervista – POI/NIH
Cervista – “Cone”
MALDI – POI/NIH
MALDI – “Cone”
<table>
<thead>
<tr>
<th>Specimen/HPV Test</th>
<th>Sensitivity $\geq$CIN 3 (%) (C.I.) (n)</th>
<th>Specificity $\geq$CIN 3 (%) (C.I.) (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal Self-collected/ Cervista HR</td>
<td>70.9% (62.7-78.3) (100/141)</td>
<td>86.1% (85.3-86.8) (7248/8415)</td>
</tr>
<tr>
<td>Endocervical / Cervista HR</td>
<td>95.0% (90.0-98.0) (134/141)</td>
<td>90.3% (89.6-90.9) (7598/8415)</td>
</tr>
<tr>
<td>Vaginal Self-collected / MALDI-TOF</td>
<td>94.3% (89.1-97.5) (133/141)</td>
<td>87.5% (86.8-88.2) (7370/8415)</td>
</tr>
<tr>
<td>Endocervical / MALDI-TOF</td>
<td>94.3% (89.1-97.5) (133/141)</td>
<td>89.4% (88.7-90.0) (7526/8415)</td>
</tr>
</tbody>
</table>
Self-Collection

- Equal in accuracy to physician collected samples
- Well-accepted by patients in multiple cultures
- Easily adapted to medically underserved sites
- Massive screening “events” possible
At this point I began to see things more clearly

- It is not necessary to think simple and small to reach the majority of the earth’s needy. Think centralized high tech, high throughput, with good quality control and the massive volumes possible with proper organization will control the per/patient cost.

- For many conditions, we spend an enormous amount of healthcare dollars identifying the people who will ultimately test negative. We need to allow the communities (and the individuals) to manage the screening and then let the healthcare workers focus on the management of the positives.
Manchay and Iquitos
Peru
The Local Organizer

• The local government, an NGO, Church group etc.
  – Must be able to identify the target population
  – Must have the funding to support the community work
  – Must have access to medical personnel and facilities for management of the positives
Teaching

Role Play

Posters

Post-course Practice
<table>
<thead>
<tr>
<th>Courses</th>
<th>Time</th>
<th>Teacher</th>
<th>Attendees</th>
<th>Poster</th>
<th>Role Play</th>
<th>Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2 ½days - to 2 days</td>
<td>Prof. (professional)</td>
<td>CLs (Community Leaders) and Promoters</td>
<td>NO</td>
<td>No structure</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>1 day – 3hrs. – 1 hr.</td>
<td>Prof.</td>
<td>CLs &amp; Promoters</td>
<td>Yes (7)</td>
<td>No structure</td>
<td>No</td>
</tr>
<tr>
<td>1</td>
<td>1 hr.</td>
<td>Prof.</td>
<td>CLs</td>
<td>Yes (7)</td>
<td>No structure</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>1 hr.</td>
<td>Prof. – Local</td>
<td>CLs and Promoters</td>
<td>Yes (7)</td>
<td>Structure</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>50 min.</td>
<td>Local</td>
<td>CLs</td>
<td>Yes (7)</td>
<td>Structure</td>
<td>Yes</td>
</tr>
<tr>
<td>2 Final Model</td>
<td>50 min.</td>
<td>Local</td>
<td>CLs and Selected Promoters</td>
<td>Yes (6)</td>
<td>Structure</td>
<td>Yes</td>
</tr>
</tbody>
</table>
The Community model uses “Expanding” Human Resources.
Self-Sampling Kit
The Development and Evaluation of a Community Based Model for Cervical Cancer Screening Based on Self-sampling

Jerome L. Belinson, Guixiang Wang, Xinfeng Qu, Hui Du, Jingjing Shen, Jiajia Xu, LiQun Zhong, Ji Yi, Xin Yi, Ruifang Wu.

Gynecologic Oncology. 2014, Jan. (epub ahead of print)
Pilot study to evaluate an internet based cervical cancer screening model based on self-sampling

- 1118 Patients
- Education
  - Registration
    - Receive Self-collection kit
    - Return kit
    - Receive results
  - Education on meaning of their results and where to receive skilled care
We have now come full circle!

Technology Development

Healthcare Delivery

Technology Development
## Sequencing Assay (n=4262 cases)

### CIN 2+

<table>
<thead>
<tr>
<th>Test</th>
<th>N</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC2 Direct</td>
<td>4262</td>
<td><strong>0.98 (0.9756, 0.9840)</strong></td>
<td><strong>0.89 (0.8790, 0.8979)</strong></td>
</tr>
<tr>
<td>MALDI Self</td>
<td>4262</td>
<td><strong>0.95 (0.9429, 0.9561)</strong></td>
<td><strong>0.89 (0.8802, 0.8990)</strong></td>
</tr>
</tbody>
</table>
| Miseq Self | 4262| **0.93 (0.9216, 0.9370)** | **0.91 (0.8983, 0.9158)****
| Pgm Self   | 4262| **0.92 (0.9110, 0.9274)** | **0.90 (0.8916, 0.9095)****

### CIN 3+

<table>
<thead>
<tr>
<th>Test</th>
<th>N</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC2 Direct</td>
<td>4262</td>
<td><strong>0.98 (0.9809, 0.9883)</strong></td>
<td><strong>0.88 (0.8718, 0.8912)</strong></td>
</tr>
<tr>
<td>MALDI Self</td>
<td>4262</td>
<td><strong>0.95 (0.9476, 0.9601)</strong></td>
<td><strong>0.88 (0.8733, 0.8926)</strong></td>
</tr>
</tbody>
</table>
| Miseq Self | 4262| **0.97 (0.9640, 0.9744)** | **0.90 (0.8919, 0.9099)****
| Pgm Self   | 4262| **0.98 (0.9809, 0.9883)** | **0.89 (0.8857, 0.9041)****

**p<0.01 vs HC2; all others NS vs HC2**
Comparison of two sequencing platforms for HPV genotyping

<table>
<thead>
<tr>
<th>Platform</th>
<th>Read Length</th>
<th>Base Pair (bp)/run</th>
<th>Samples per run</th>
<th>Time per run(^1)</th>
<th>Labor Demand(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MiSeq (V1)</td>
<td>2 × 150bp</td>
<td>800M-900M</td>
<td>1248</td>
<td>27h</td>
<td>4-5</td>
</tr>
<tr>
<td>PGM (318 chip)</td>
<td>200bp</td>
<td>800M-1000M</td>
<td>1440</td>
<td>4.5h</td>
<td>3-4</td>
</tr>
</tbody>
</table>

\(^1\) The sequencers can work continuously. A single run is preceded by PCR and library preparation. After the run is data analysis and results reporting with total laboratory time 3-5 days. The current laboratory maximum throughput is about 6000 per day.

\(^2\) not including DNA extraction/elution
Cumulative Methylation Patterns During Tumorigenesis

Normal → Low grade dysplasia → High grade dysplasia → Invasive cancer → Metastasis

TSG1 TSG2 TSG3 TSG4

Methylation
100 HPV+ patients

HPV+  CIN 2+

23-25 M-HPV+ patients

M-HPV+  CIN 2+
A New Solid Media Specimen Transport Card

- Developed by Hyde Biomedical in Anhui Province, China in collaboration with POI.
- Functions are similar to iFTA elute (G.E.)
- Key Differences:
  - 1. A fraction of the cost
  - 2. Does NOT change color in high humidity environments
It is all about “the system”

New and exciting technologies only become real innovations when they are integrated into a system or a new system is developed around them.
The New Paradigm

- Community based screening using self-collection for high risk HPV
- Non-liquid transport media
- Centralized processing (good QC)
- Highly sensitive and specific high throughput low cost per case assay
- Healthcare resources focused on the management of the positives
COLLABORATORS

Staff - Bing Yang, Charles Biscotti, Jennifer Brainard, Andres Chiesa-Vottero, Christine Booth.

Fellows – Andrew Green, Pedro Escobar, Luis Rojas, Nabila Rasool, Lucybeth Nieves*, David Starks*, Kim Levinson, Sara Goodrich, Carolina Abuelo, Kate Maurer

Students – Patrick Elliott*, Eunice Chyung, Ali Usifoh*, Cynthia Arvizo

International – Great collaborating PI’s, physicians, scientists, and students from China, Peru, Mexico, India, and the Dominican Republic.