

THE POWER FOR HEALTH



PapilloCheck® HPV-Screening

DNA-Chip for the identification of 24 types of genital HPV

PapilloCheck®:

A head start in HPV screening



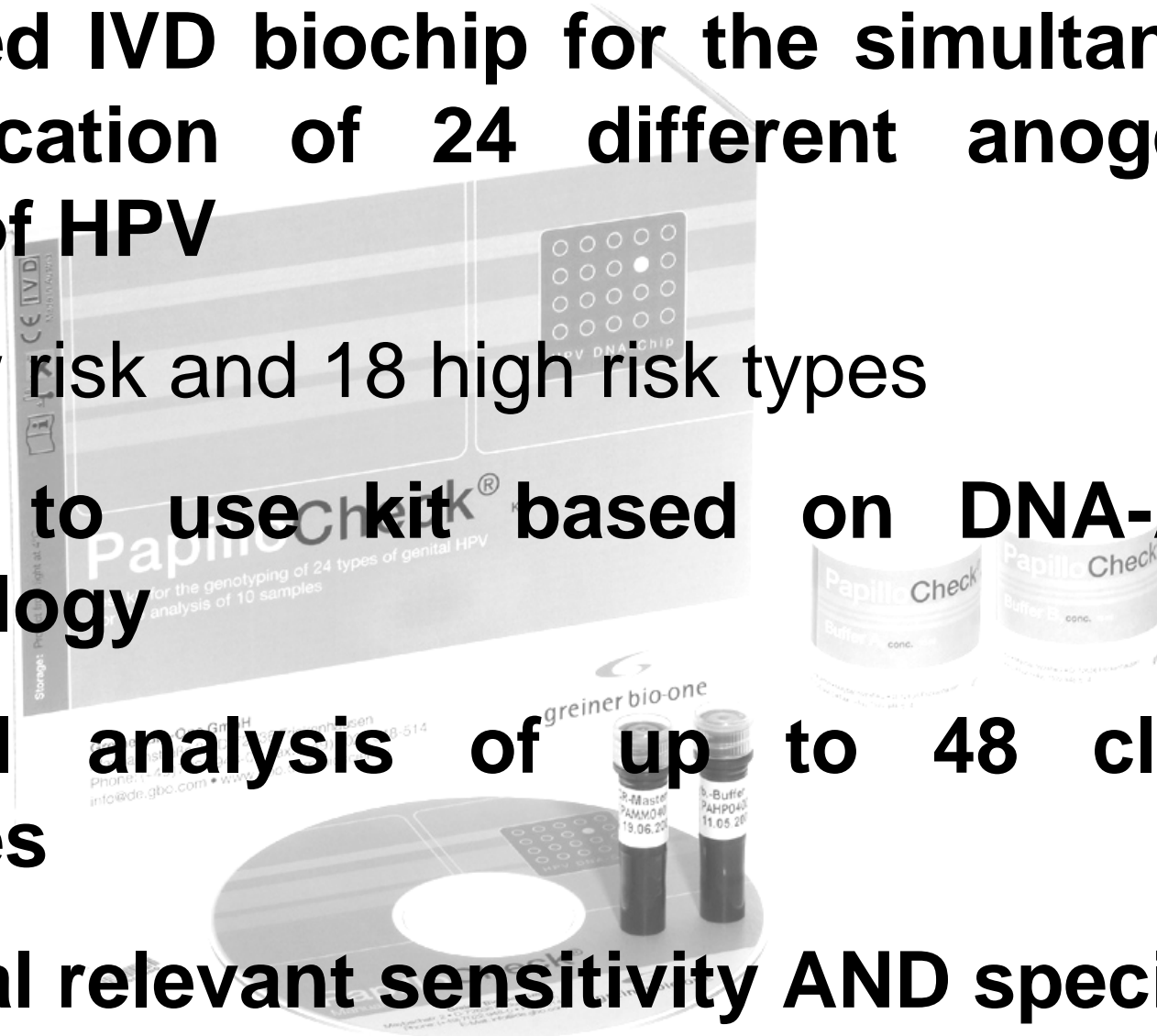
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PapilloCheck[®]: A head start in HPV screening



- ✓ **Certified IVD biochip for the simultaneous identification of 24 different anogenital types of HPV**
 - 6 low risk and 18 high risk types
- ✓ **Ready to use kit[®] based on DNA-Array technology**
- ✓ **Parallel analysis of up to 48 clinical samples**
- ✓ **Clinical relevant sensitivity AND specificity**



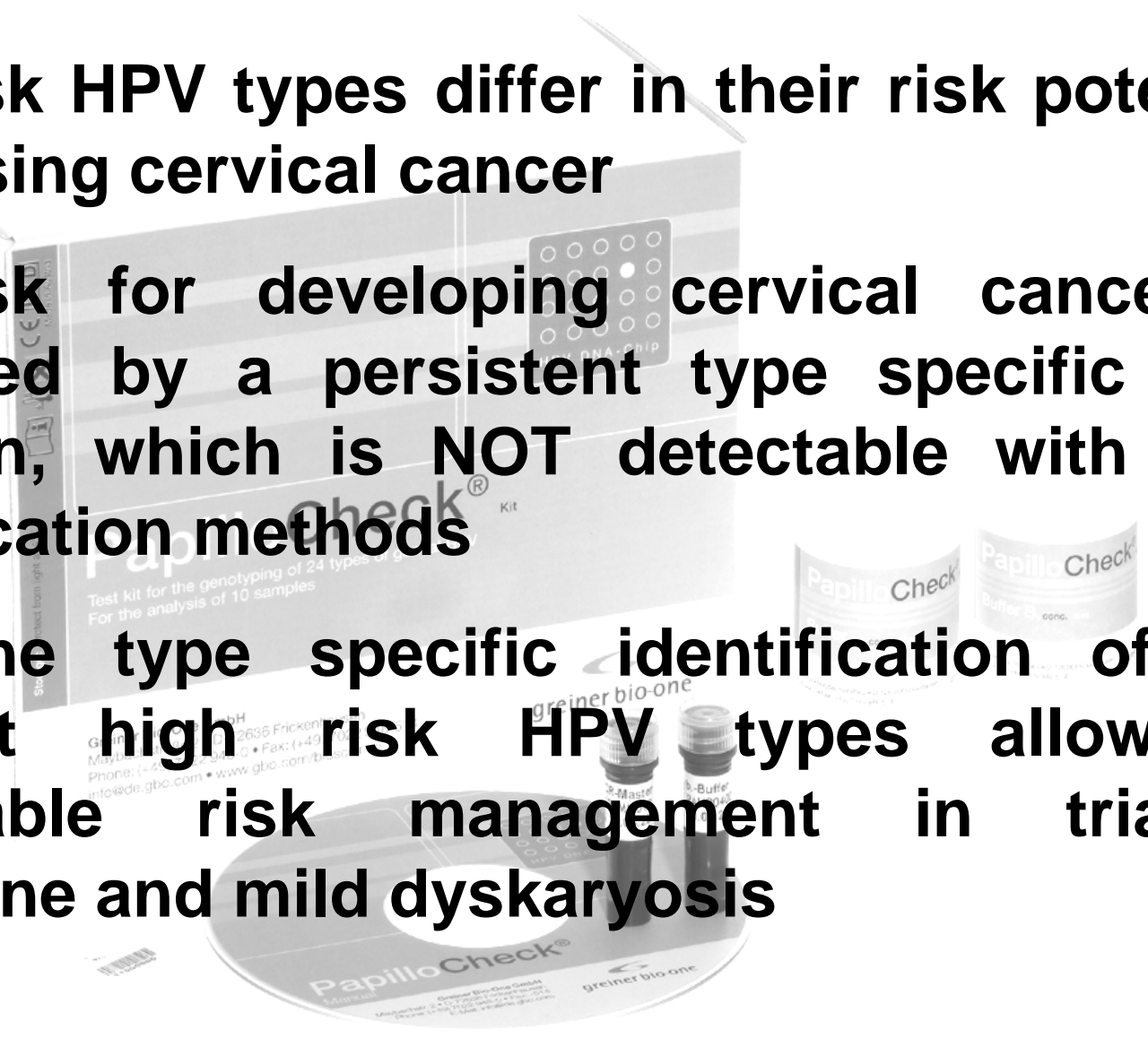
PapilloCheck®:

Why is HPV genotyping essential ?



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- ✓ High risk HPV types differ in their risk potential for causing cervical cancer
- ✓ The risk for developing cervical cancer is increased by a persistent type specific HPV infection, which is NOT detectable with HPV classification methods
- ✓ Only the type specific identification of the different high risk HPV types allows a reasonable risk management in triaging borderline and mild dyskaryosis



PapilloCheck[®]: Detectable HPV-Types



✓ Detectable low risk HPV types

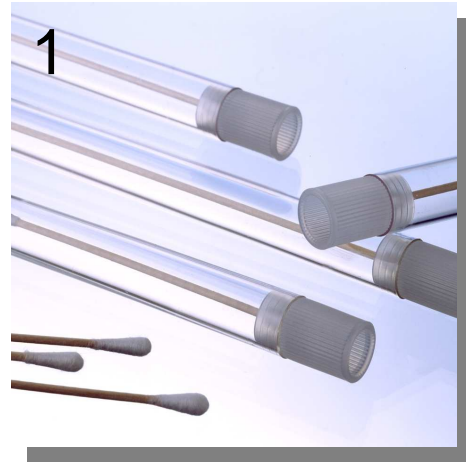
6	11	40	42	43	44
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✓ Detectable high risk HPV types

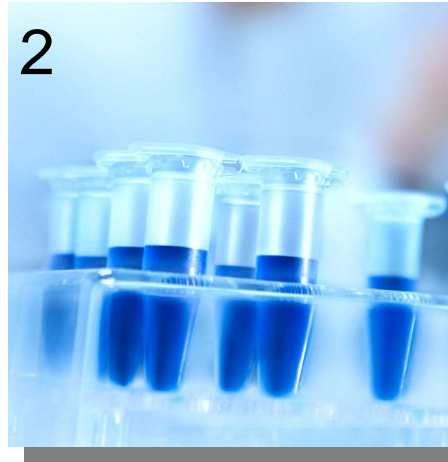
16	18	31	33	35	39	45
51	52	53	56	58	59	66
68	70	73	82			

PapilloCheck[®]: Fast and Reliable

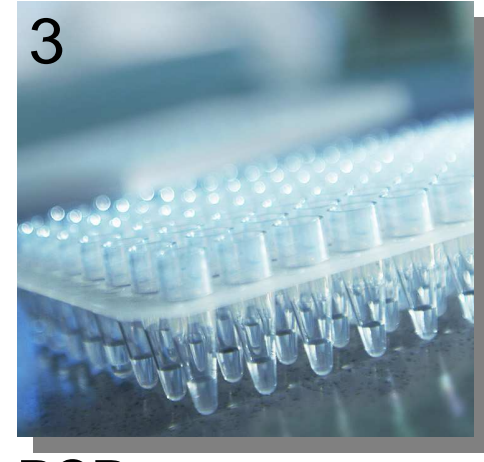
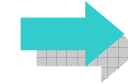

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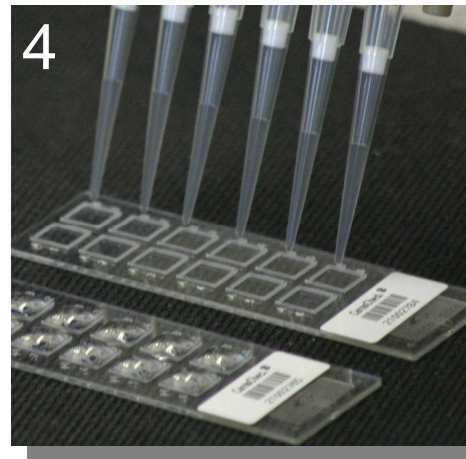
1
Sample collection
10 min



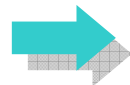
2
DNA extraction
30 min



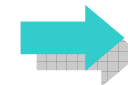
3
PCR
2.5 h



4
Hybridisation, r.t.
15 min



5
Washing,
5 min

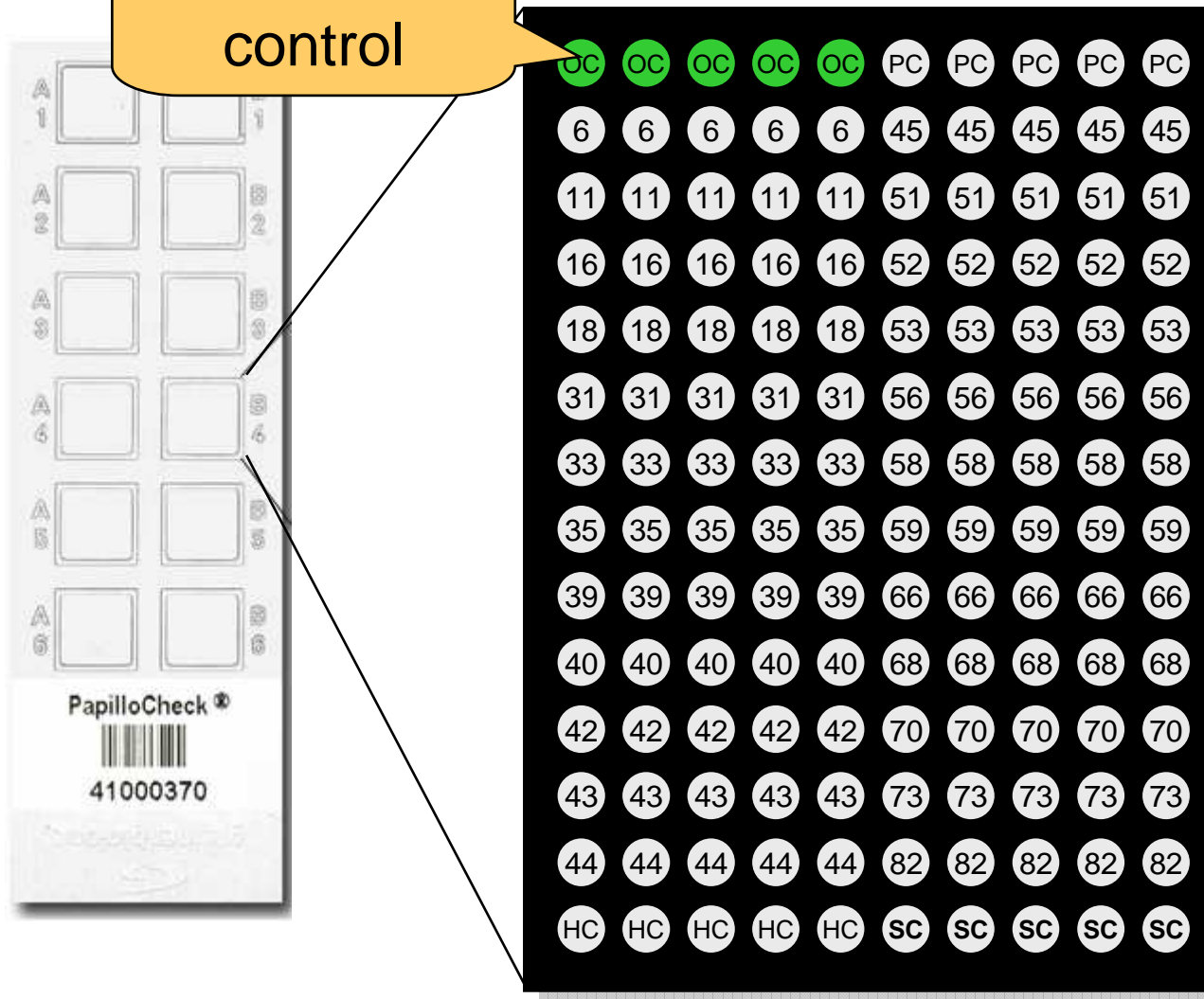


6
Evaluation
15 min

- ✓ **Comprehensive “on chip” control systems for high quality results**
 - **Control I:** Orientation controls for optimized analysis.

PapilloCheck[®]: On Chip Controls I

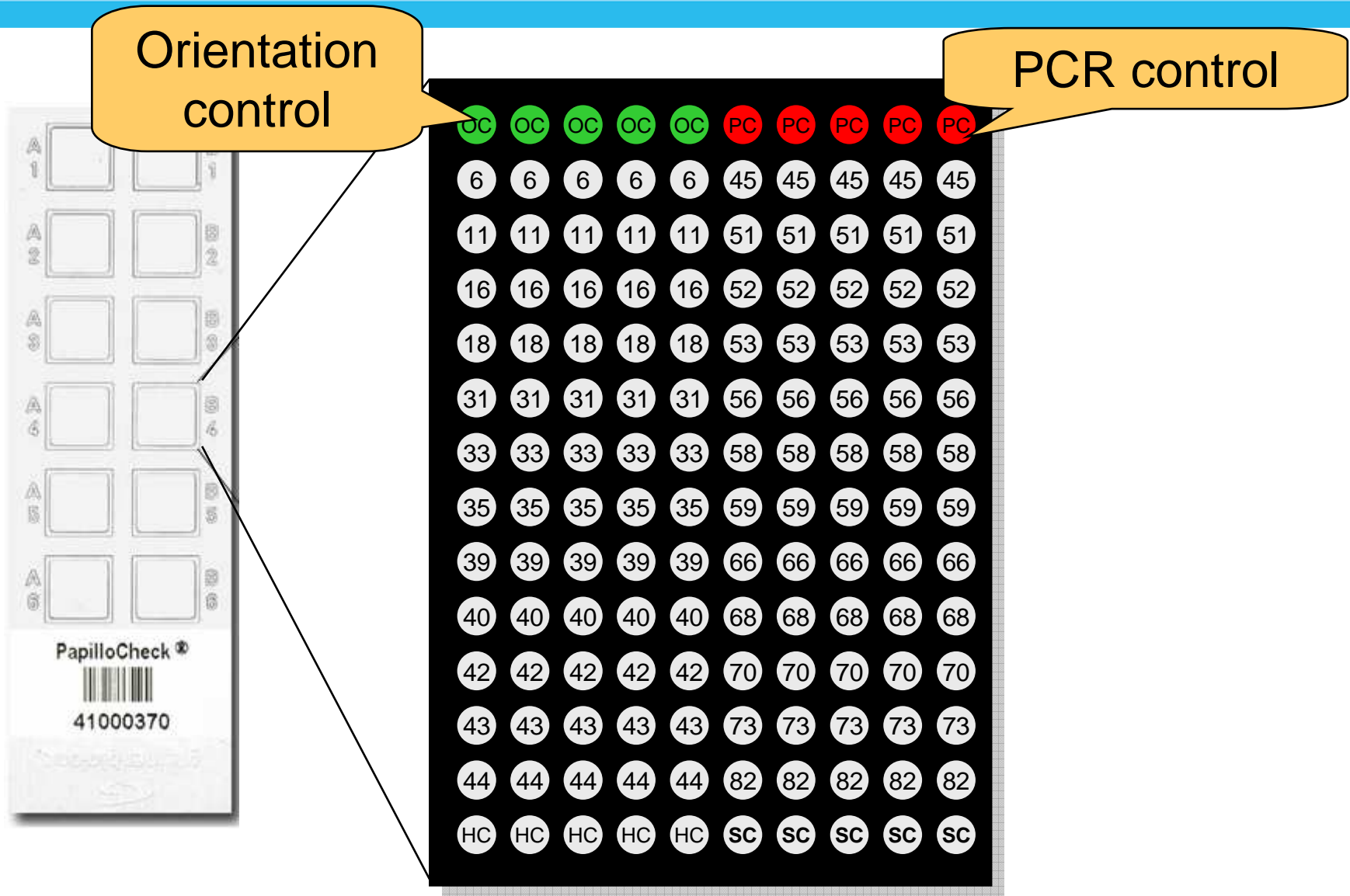
Orientation control



✓ Comprehensive “on chip” control systems for high quality results

- **Control I:** Orientation controls for optimized analysis.
- **Control II:** Quality control of the PCR

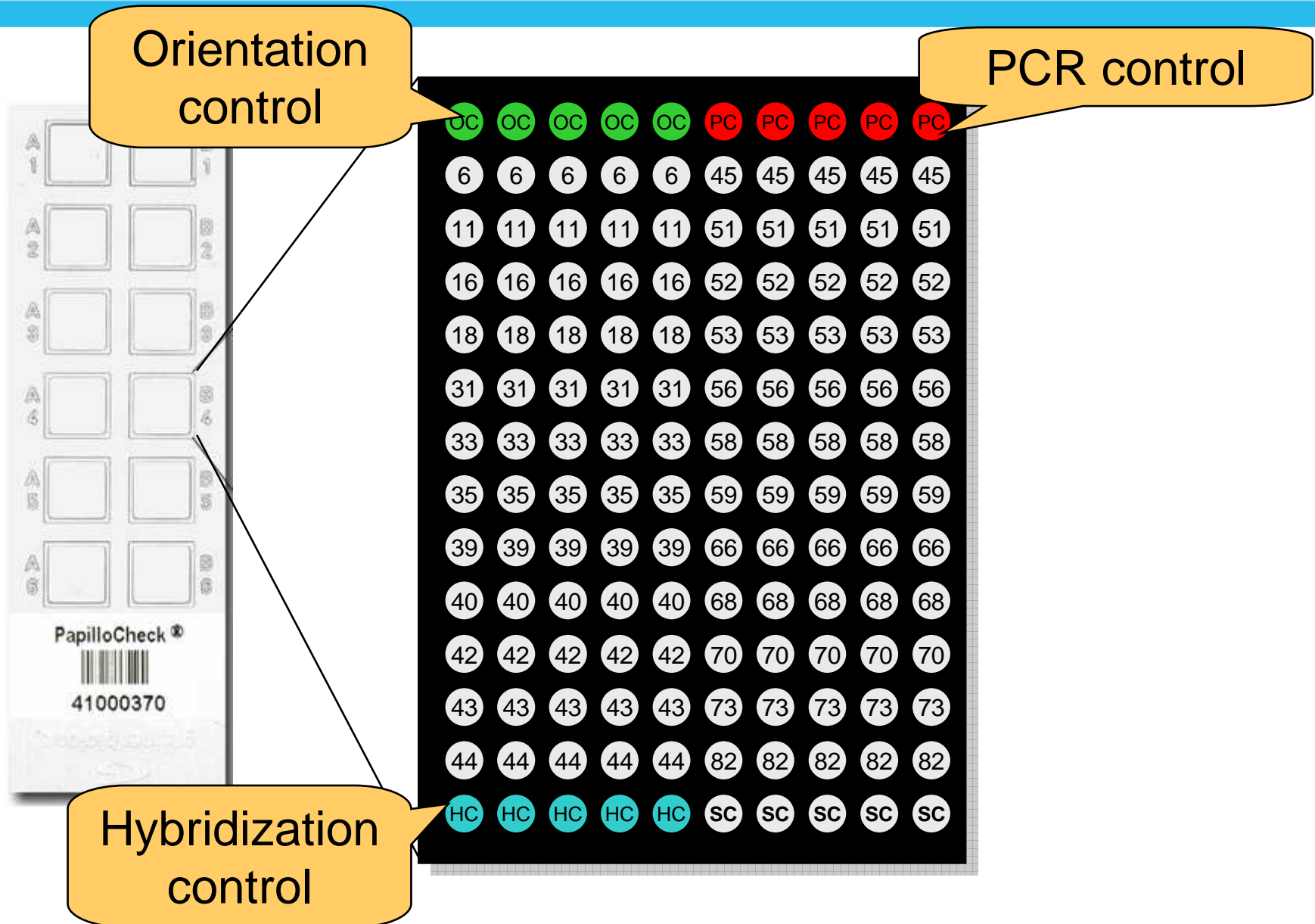
PapilloCheck[®]: On Chip Controls II



✓ Comprehensive “on chip” control systems for high quality results

- **Control I:** Orientation controls for optimized analysis.
- **Control II:** Quality control of the PCR
- **Control III:** Quality control of the Hybridization

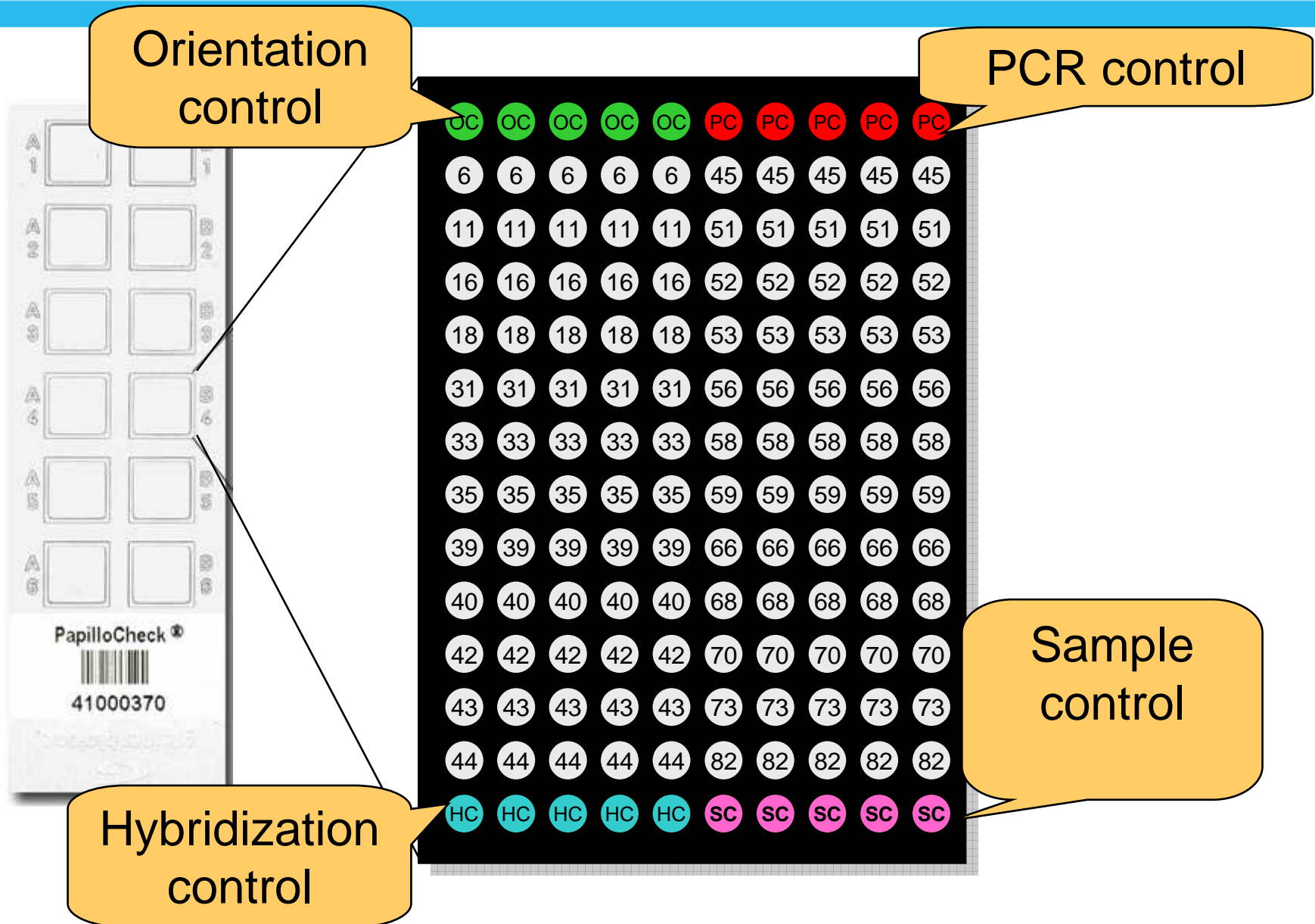
PapilloCheck[®]: On Chip Controls III



✓ Comprehensive “on chip” control systems for high quality results

- **Control I:** Orientation controls for optimized analysis.
- **Control II:** Quality control of the PCR
- **Control III:** Quality control of the Hybridization
- **Control IV:** Quality control of the sample

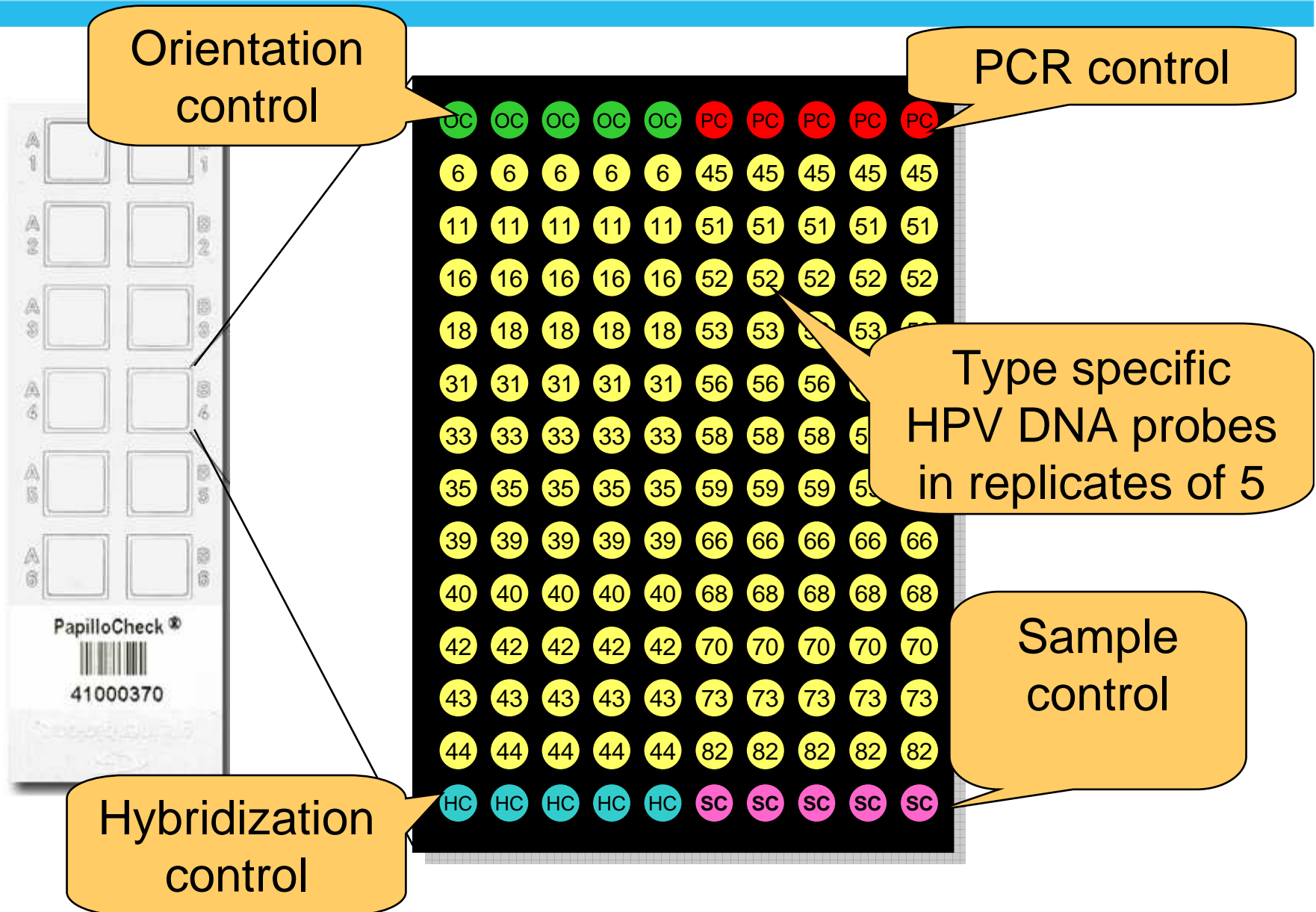
PapilloCheck[®]: On Chip Controls IV



✓ Comprehensive “on chip” control systems for high quality results

- **Control I:** Orientation controls for optimized analysis.
- **Control II:** Quality control of the PCR
- **Control III:** Quality control of the Hybridization
- **Control IV:** Quality control of the sample
- **Control V:** Quality control of the complete DNA-array

PapilloCheck[®]: On Chip Controls V



PapilloCheck[®]: Biochip Features

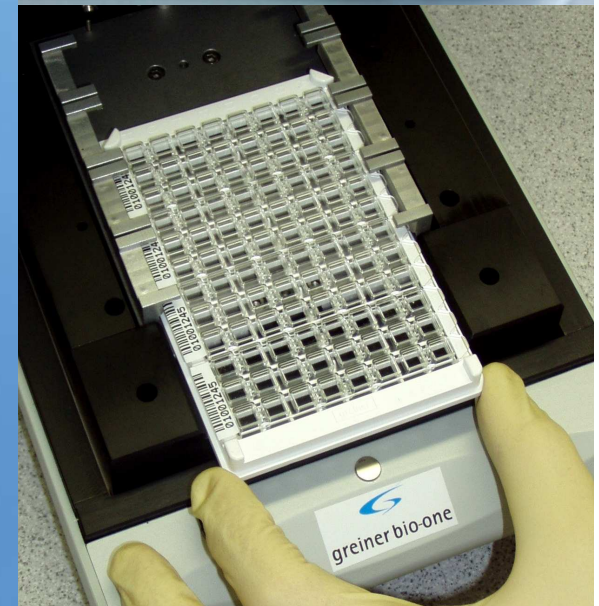
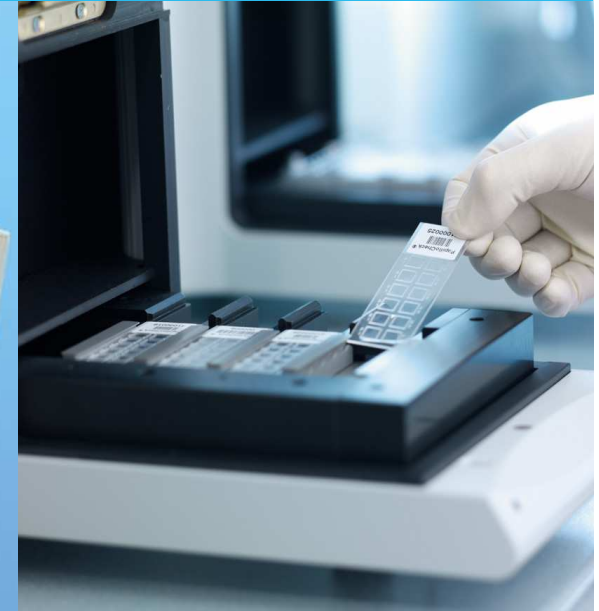
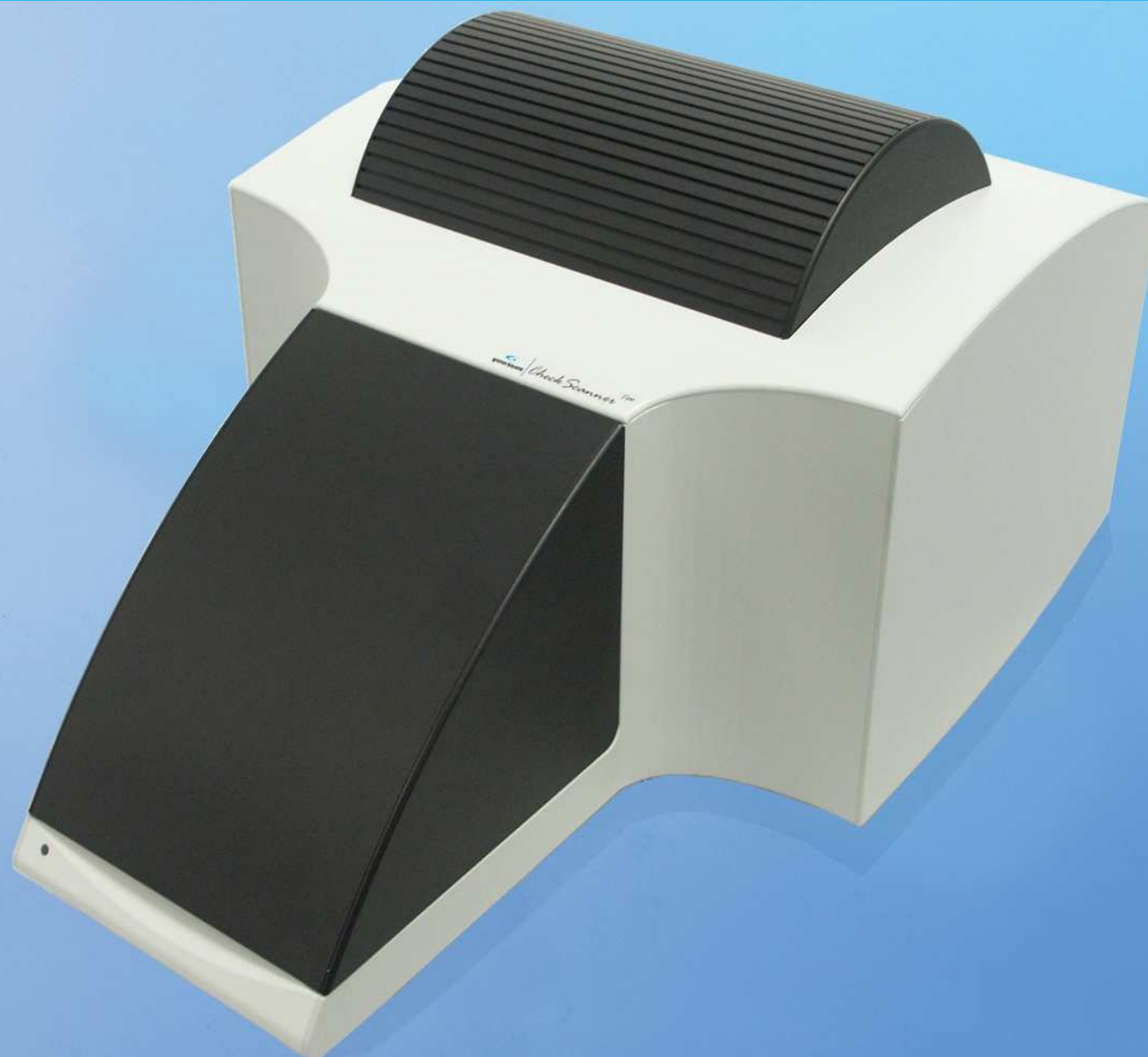


- ✓ **Comprehensive “on chip” control systems for high quality results**
- ✓ **Accurate and fast analysis of the PapilloCheck[®] by the CheckScanner[™] and CheckReport[™] software**

CheckScanner™



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CheckScanner™:

Accurate measurement



- ✓ **Two laser scanner with excitation wavelength of 532 nm and 635 nm**
- ✓ **Motorized focus adjustment**
- ✓ **Pixel resolution: 4 to 100 μm adjustable**
- ✓ **Sensitivity: $< 0,1$ fluorescent molecule/ μm^2**
- ✓ **16-bit dynamic range, linear over 4 decades**
- ✓ **Automatic analysis of 4 HTA™ slides or 1 HTA™ plate by barcode identification**
- ✓ **Fully integrated communication with CheckReport™ software for data analysis**

CheckReport™ Software:

Accurate and Fast Result Generation



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- ✓ **CheckReport™ (CR) consists of three modules: CR™SampleSheet, CR™Results and CR™Admin**
- ✓ **The CheckReport software allows a semi-automatic biochip evaluation and data administration required for a diagnostic set-up**
- ✓ **Evaluation results are converted into simple, user friendly graphics or tables**

CheckReport™ SampleSheet: Easy and Fast Patient Assignment



A sample sheet
assigns patient
samples to chips
or stripes

41
41414141

Sample Annotation
Selected Test: 1
Annotations: Complete

Protocol Schmidt
Date 14.12.2005
Test Number 01
Patient Alaun
Sample ID 014001
Negative Control

SampleSheet Functions

Comments

CheckReport™ Result: Simple Analysis



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Visual Image
Inspection of
the DNA-array

HTA™ 12
Slide
Overview

The screenshot displays the CheckReport software interface. On the left, a list of test samples is shown with status indicators (checkmarks, X, and empty boxes). The central area features a grid of spots, with some spots highlighted in orange. On the right, a detailed view of a 6x2 grid of spots is shown, with a barcode below it. The bottom right corner contains a 'Display Control' panel with zoom, channels, and image manipulation settings.

Assessment: Grid

Test

- Test: Sample 1
- Test: Sample 7
- Test: Sample 2
- Test: Sample 8
- Test: Sample 3
- Test: Sample 9
- Test: Sample 4
- Test: Sample 10
- Test: Sample 5
- Test: Sample 11
- Test: Sample 6
- Test: Sample 12

Spot Information

Check Controls Create Reports

Display Control

Zoom: 100%

Channels

Image Manipulation

Brightness: 50

Contrast: 73

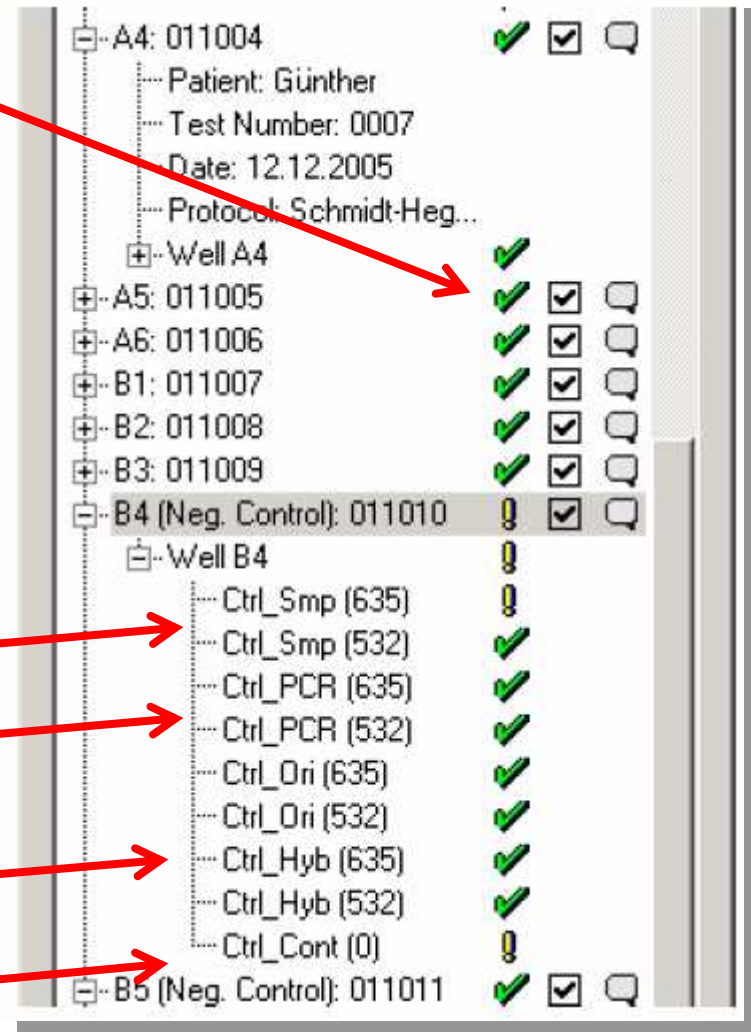
Neutral Optimal

Automatic
Quality
Assessment

CheckReport™ Result: Automatic Quality Assessment

- ✓ CheckReportResults automatically assesses the quality of each result.
- ✓ Controls are standardized probes on each chip, allowing the quality assessment of the:

- Sample material
- PCR
- Hybridization
- Contamination status



[-] A4: 011004	✓	☑	🗨
--- Patient: Günther			
--- Test Number: 0007			
--- Date: 12.12.2005			
--- Protocol: Schmidt-Heg...			
[+] Well A4	✓		
[+] A5: 011005	✓	☑	🗨
[+] A6: 011006	✓	☑	🗨
[+] B1: 011007	✓	☑	🗨
[+] B2: 011008	✓	☑	🗨
[+] B3: 011009	✓	☑	🗨
[-] B4 (Neg. Control): 011010	!	☑	🗨
[-] Well B4	!		
--- Ctrl_Smp (635)	!		
--- Ctrl_Smp (532)	✓		
--- Ctrl_PCR (635)	✓		
--- Ctrl_PCR (532)	✓		
--- Ctrl_Ori (635)	✓		
--- Ctrl_Ori (532)	✓		
--- Ctrl_Hyb (635)	✓		
--- Ctrl_Hyb (532)	✓		
--- Ctrl_Cont (0)	!		
[-] B5 (Neg. Control): 011011	✓	☑	🗨

CheckReport™ Result: Simple Reports

✓ 1. Clear overview of all control results

PapilloCheck Evaluation

Sample Annotation:

Chip Number: 41000383
Well: A1
Sample ID: C2365
Patient: N.N.

Control	Channel	Number of Spots	SNR	Status
Hybridization Control	532	5	525.4	OK
Hybridization Control	635	5	0	OK
Orientation Control	532	5	314.5	OK
Orientation Control	635	5	0	OK
PCR Control	532	5	157.3	OK
PCR Control	635	5	1766.1	OK
Sample Control	532	5	300.6	OK
Sample Control	635	5	1595.9	OK

CheckReport™ Result: Simple Reports



✓ 2. Clear overview of all sample results

Sample Annotation:	
Chip Number:	41000383
Well:	A1
Sample ID:	C2365
Patient:	N.N.

HPV Type	Result
HPV6	negative
HPV11	negative
HPV16	negative
HPV18	negative
HPV31	negative
HPV33	negative
HPV35	negative
HPV39	negative
HPV40	negative
HPV42	negative
HPV43	negative
HPV44/55	negative
HPV45	negative
HPV51	negative
HPV58	negative

HPV type

Result

Clinical Validation (Biopsies)

- ✓ **298 cervical biopsies (45 \geq CIN2, 253 $<$ CIN2) with a valid histology result were analyzed with PapilloCheck[®]**

		Result of biopsy CIN2 or higher		
		+	-	total
Result of HPV-Test	+	44	192	236
	-	1	61	62
	total	45	253	298

**Papillo-
Check**

Sensitivity %	97.8
Specificity %	24.1
disease prevalence %	15.1
PPV	18.6
NPV	98.4

Clinical Validation (Colposcopy)

- ✓ **380 colposcopic cervical examinations (250 colposcopy „negative“, 130 colposcopy “positive”) were analyzed with PapilloCheck®**

		Result of colposcopy low grade lesion or higher		
		+	-	total
Result of HPV-Test	+	119	180	299
	-	11	70	81
	total	130	250	380

**Papillo-
Check**

Sensitivity %	91.5
Specificity %	28.0
disease prevalence %	34.2
PPV	39.8
NPV	86.4

- ✓ **The analytical validation of the PapilloCheck[®] includes:**
 - Sensitivity (limit of detection)
 - Specificity (HPV types, bacteria)
 - Reproducibility

- ✓ **Analytical Sensitivity (limit of detection, CI 95%):**
 - 30 – 150 plasmid copies/PCR (6-24 measurements/dilution)

- ✓ **Analytical Specificity:**
 - Hybridization of 2.12×10^6 copies of each of **39!** different HPV types:
 - HPV6, HPV11, HPV13, HPV16, HPV18, HPV26, HPV30, HPV31, HPV33, HPV34, HPV35, HPV39, HPV40, HPV42, HPV43, HPV44, HPV45, HPV51, HPV52, HPV53, HPV54, HPV55, HPV56, HPV58, HPV59, HPV61, HPV66, HPV67, HPV68, HPV69, HPV70, HPV71, HPV73, HPV74, HPV81, HPV82, HPV84, HPV85, HPV91.
 - With the exception of HPV 44/55 and HPV 11/13 NO cross reaction of probes
 - Observed cross reactions are covered by the CheckReport[®] software

- ✓ **No cross-reactivity of the array probes with roughly 100 different bacterial types, commonly found in the female anogenital tract, have been observed**

Acinetobacter baumannii ,*Acinetobacter calcoaceticus* ,*Acinetobacter lwoffii* ,*Actinobacillus actinomycetemcomitans* Serovar c ,*Actinomyces odontolyticus* ,*Actinomyces viscosus* ,*Bacillus subtilis* ,*Bifidobacterium adolescentis* ,*Bifidobacterium breve* ,*Campylobacter concisus* ,*Campylobacter gracilis* ,*Campylobacter rectus* ,*Candida albicans* ,*Capnocytophaga gingivalis* ,*Capnocytophaga ochracea* ,*Capnocytophaga sputigena* ,*Citrobacter amalonaticus* ,*Citrobacter freundii* ,*Citrobacter freundii* ,*Citrobacter koseri* ,*Citrobacter koseri* ,*Clostridium difficile* ,*Clostridium perfringens* ,*Eikenella corrodens* ,*Enterobacter aerogenes* ,*Enterobacter cloacae* ,*Enterobacter sakazakii* ,*Enterococcus durans* ,*Enterococcus faecali* ,*Enterococcus faecium* ,*Escherichia coli* ,*Eubacterium nodatum* ,*Fusobacterium nucleatum* ,*Gardnerella vaginalis* ,*Hafnia alvei* ,*Kingella denitrificans* ,*Klebsiella oxytoca* ,*Klebsiella pneumoniae* ,*Lactobacillus casei* ,*Lactobacillus crispatus* ,*Lactobacillus gasseri* ,*Lactobacillus iners* ,*Lactobacillus rhamnosus* ,*Lactobacillus vaginalis* ,*Mogibacterium timidum* ,*Morganella morganii* ,*Mycoplasma hominis* ,*Mycoplasma buccale* ,*Mycoplasma faucium* ,*Mycoplasma fermentans* ,*Mycoplasma genitalium* ,*Mycoplasma orale* ,*Mycoplasma pirum* ,*Mycoplasma salivarium* ,*Mycoplasma pneumoniae* ,*Neisseria elongata* ,*Neisseria gonorrhoeae* ,*Peptoniphilus asaccharolyticus* ,*Peptostreptococcus anaerobius* ,*Peptostreptococcus micros* ,*Porphyromonas gingivalis* ,*Prevotella intermedia* ,*Prevotella nigrescens* ,*Proteus hauseri* ,*Proteus mirabilis* ,*Proteus vulgaris* ,*Proteus vulgaris* ,*Pseudomonas aeruginosa* ,*Pseudomonas fluorescens* ,*Pseudomonas fluorescens* ,*Pseudomonas putida* ,*Serratia marcescens* ,*Staphylococcus aureus* ssp. aureus ,*Staphylococcus epidermidis* ,*Staphylococcus haemolyticus* ,*Staphylococcus saprophyticus* ,*Stenotrophomonas maltophilia* ,*Streptococcus agalactiae* ,*Streptococcus constellatus* ,*Streptococcus criceti* ,*Streptococcus cristatus* ,*Streptococcus gordonii* ,*Streptococcus intermedius* ,*Streptococcus mitis* ,*Streptococcus mutans* ,*Streptococcus oralis* ,*Streptococcus parasanguinis* ,*Streptococcus pneumoniae* ,*Streptococcus pyogenes* ,*Streptococcus salivarius* ,*Streptococcus sanguinis* ,*Streptococcus sobrinus* ,*Tannerella forsythensis* (former: *Bacteroides forsythus*) ,*Treponema denticola* ,*Ureaplasma urealyticum* ,*Veillonella parvula* .

PapilloCheck[®]: A head start in HPV screening



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