

Emerging Laboratory Diagnostic Options for Sexually-transmitted Infections

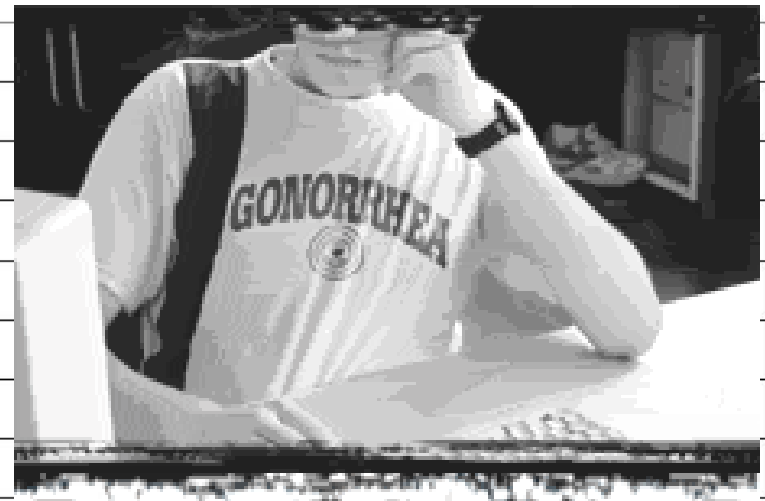
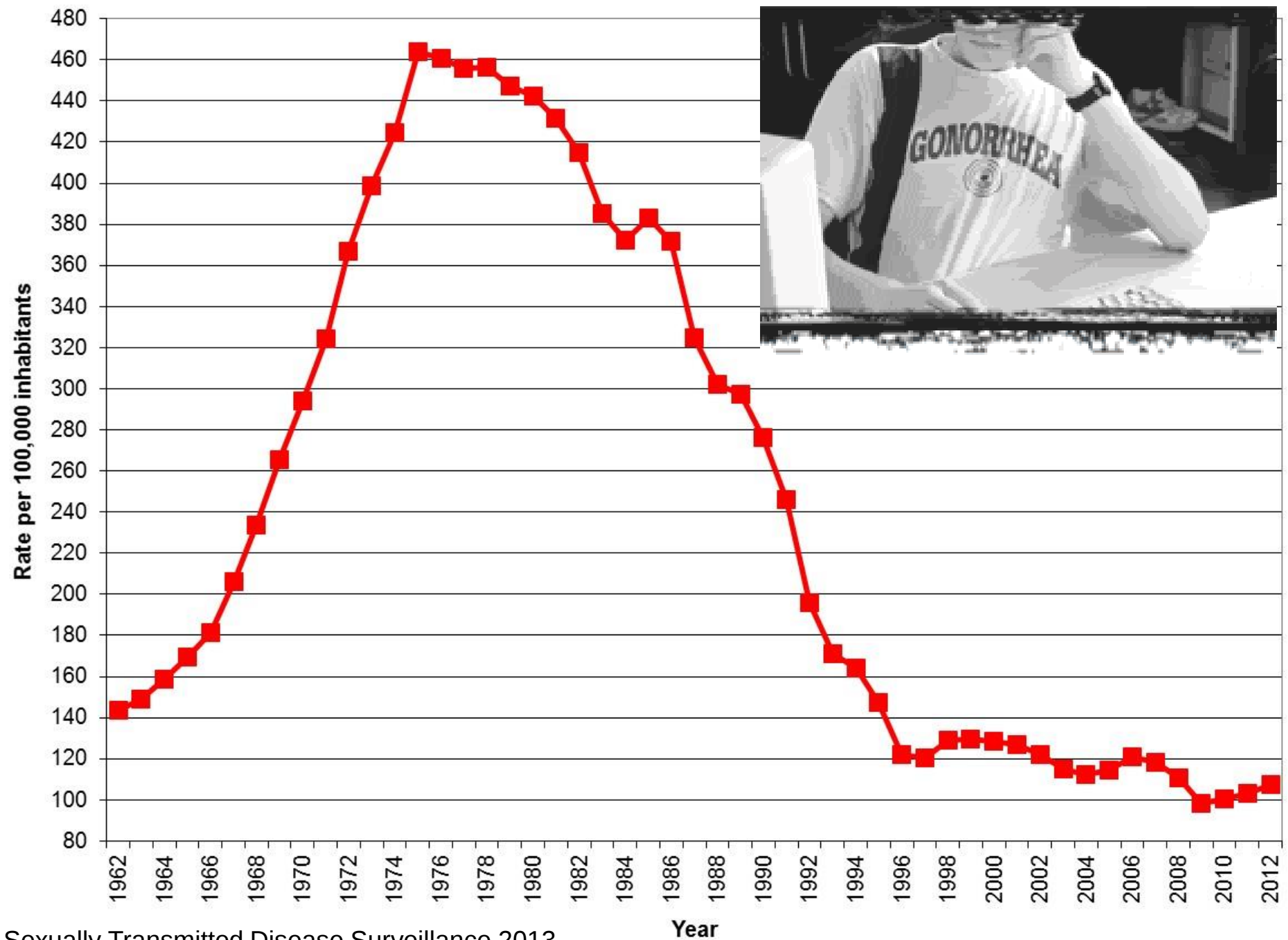


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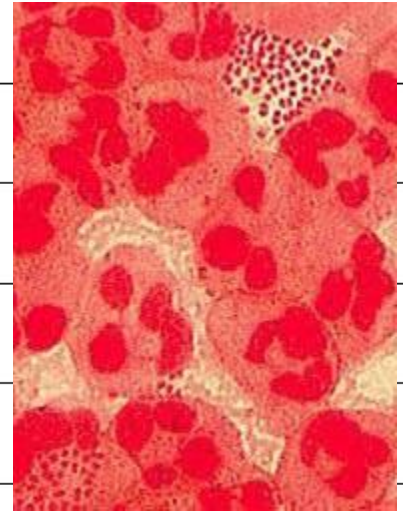
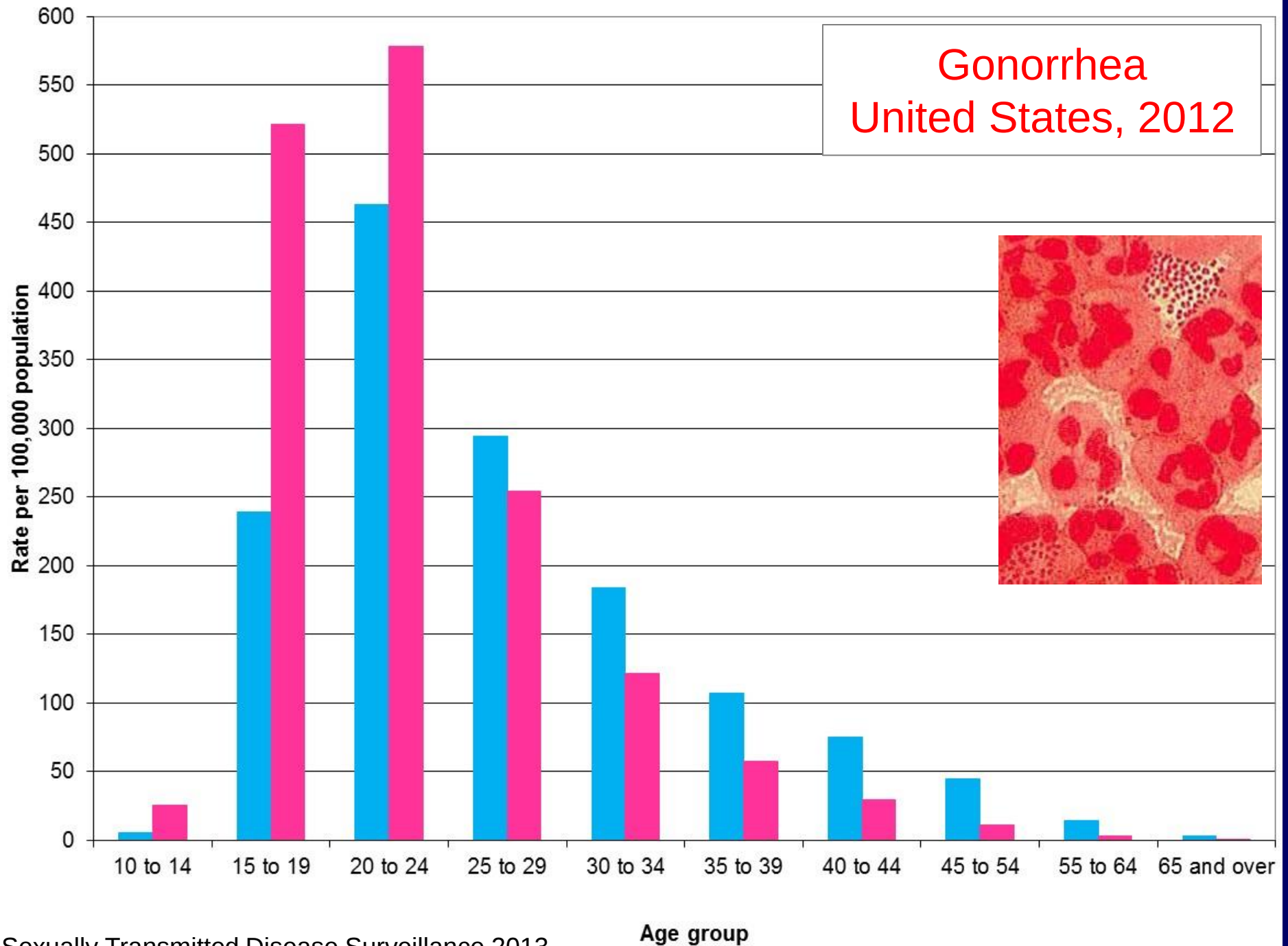


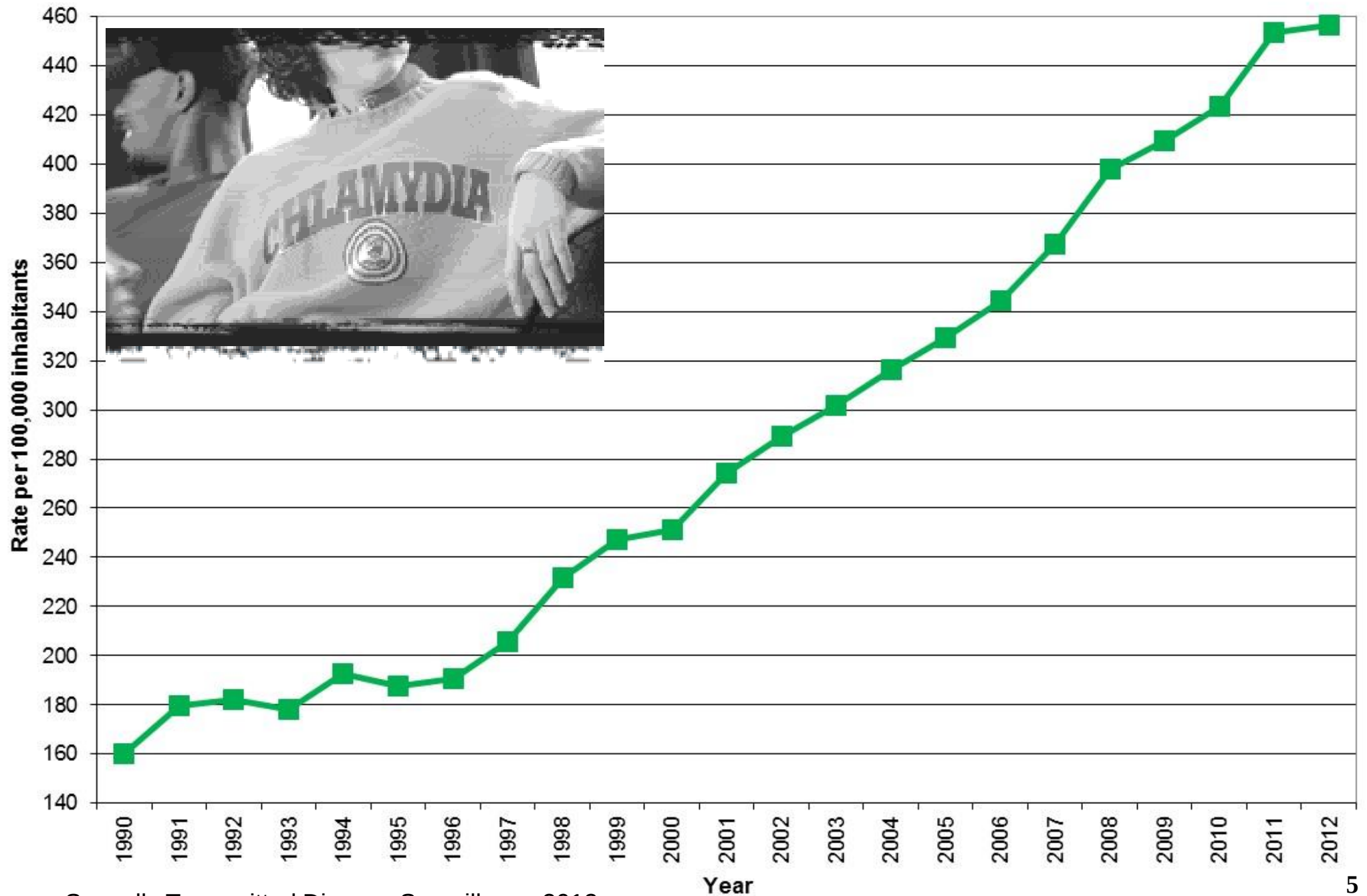
OBJECTIVES

- I. Appreciate the changing epidemiology of trichomoniasis and clinician ordering patterns on the basis of improved laboratory diagnostics
- II. Characterize the distribution of *Mycoplasma genitalium* infection in women and men on the basis of a new diagnostic option
- III. Describe the evolution of molecular screening for human papillomavirus and application to cervical cytology

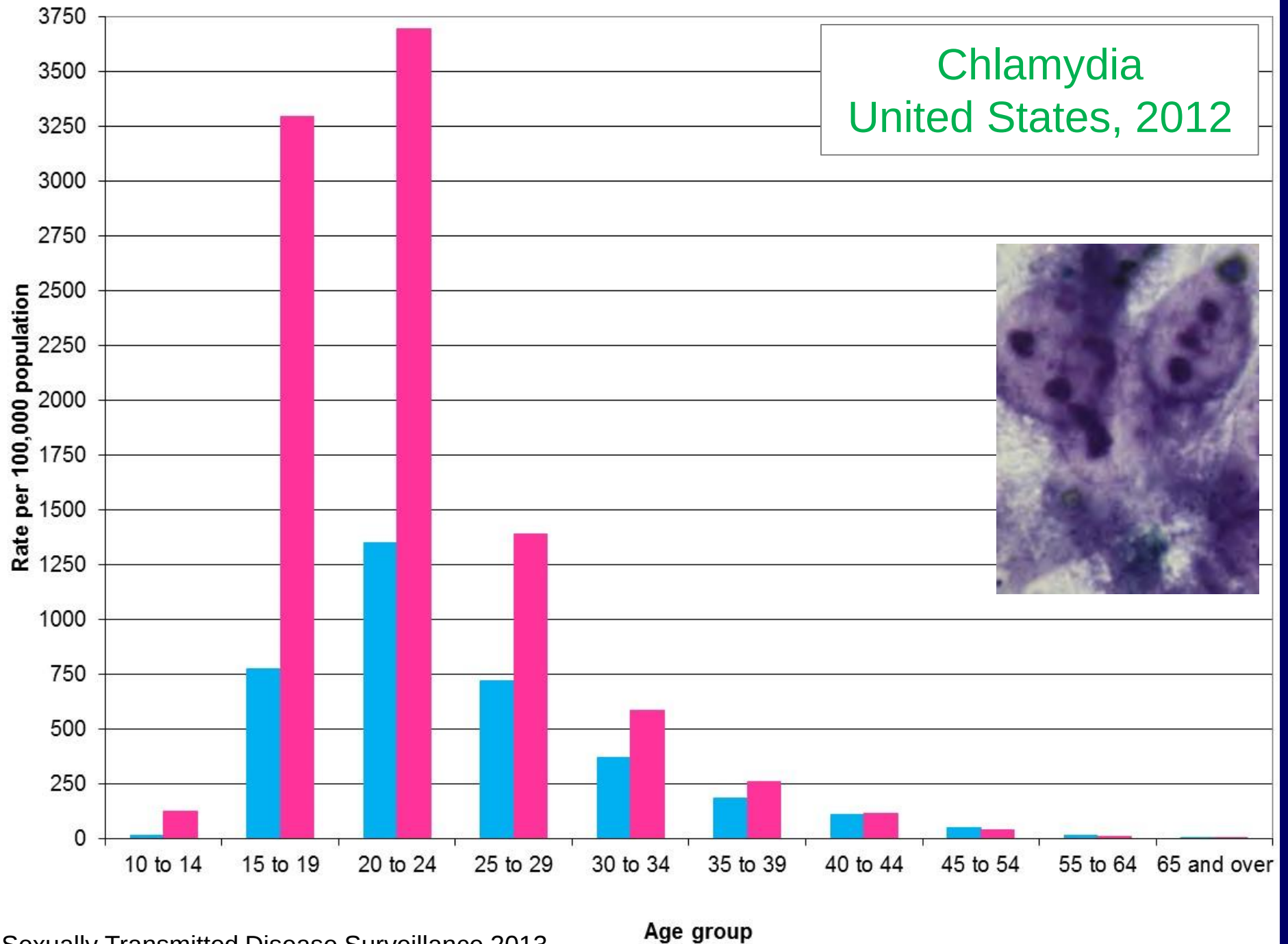


Gonorrhea United States, 2012





Chlamydia United States, 2012



Confirming Positive Results of Nucleic Acid Amplification Tests (NAATs) for *Chlamydia trachomatis*: All NAATs Are Not Created Equal

J. Schachter,^{1*} E. W. Hook,² D. H. Martin,³ D. Willis,⁴ P. Fine,⁵ D. Fuller,⁶ J. Jordan,⁷
W. M. Janda,⁸ and M. Chernesky⁹

University of California, San Francisco, California¹; University of Alabama, Birmingham, Alabama²; Louisiana State University Medical Center, New Orleans, Louisiana³; Florida State Department of Health, Jacksonville, Florida⁴; Planned Parenthood Foundation of Houston and Southeast Texas, Houston, Texas⁵; Wishard Memorial Hospital, Indianapolis, Indiana⁶; Magee-Womens Research Institute, Pittsburgh, Pennsylvania⁷; University of Illinois, Chicago, Illinois⁸; and St. Joseph's Health Care Regional Virology and Chlamydiology Laboratory, Hamilton, Ontario, Canada⁹

Received 4 August 2004/Returned for modification 7 October 2004/Accepted 14 November 2004

In vitro CHALLENGE *C. trachomatis*

Elementary Bodies	TMA Result		PCR Result
	Light Units (x1000)	Interpretation	
200	1217	detected	detected
20	1111	detected	detected
2	1062	detected	not detected
0.2	878	detected	not detected
0.02	288	detected	<i>not tested</i>
0.002	12	not detected	<i>not tested</i>
0.0002	14	not detected	<i>not tested</i>
0.00002	13	not detected	<i>not tested</i>

EXTRA-UROGENITAL GONOCOCCUS

Source	Modality	Sensitivity (%)	Specificity (%)
Pharynx	Culture	60.0	100.0
	DNA amplification (PCR)	60.0	78.9
	RNA amplification (TMA)	95.0	100.0
Rectum	Culture	50.0	100.0
	DNA amplification (PCR)	44.4	99.5
	RNA amplification (TMA)	100.0	99.5

EXTRA-UROGENITAL TMA (since '10)

Gender	Source	n	Detection Rate (%)	
			<i>C. trachomatis</i>	<i>N. gonorrhoeae</i>
Female	Pharynx	167	1.2	1.8
	Rectum	51	3.9	2.0
Male	Pharynx	3910	1.0	3.8
	Rectum	1864	7.0	7.0

CHLAMYDIA TRENDING

Metropolitan Statistical Area	Mean Annual Rank	Aggregate Rate/100,000
Memphis	1.22	792.5
Milwaukee	2.00	678.0
Virginia Beach-Norfolk	4.11	566.0
Philadelphia	9.44	474.3
Indianapolis	10.33	480.1
Jacksonville	10.78	462.2
San Antonio	10.78	468.6
Richmond	11.22	466.6
Saint Louis	11.33	464.4
Birmingham	11.56	476.1
United States	NA	382.3

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"Gonorrhea, syphilis, chlamydia, herpes,
HIV positive, genital warts..."

"Trich is just an itching disease;
why should I care?"



SOCIAL/PUBLIC HEALTH I

- HIV transmission facilitated by *T. vaginalis* infection

Sex. Transm. Dis. **31**: 541-547; 2004

- 2.57 relative risk for per-act probability of HIV transmission for *T. vaginalis*-positive women at start of two-year surveillance ($P = 0.002$)

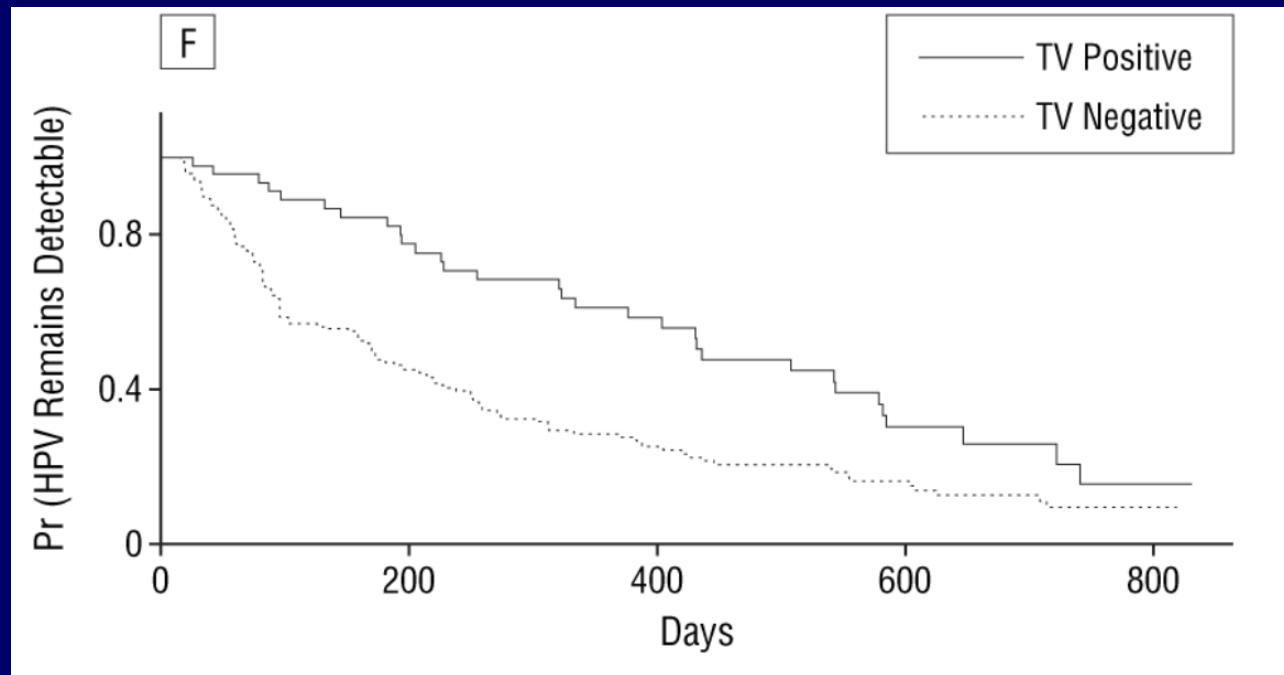
J. Infect. Dis. **205**: 358-365; 2012

- Estimated \$167 million for *T. vaginalis*-attributable HIV infection

Sex. Transm. Dis. **31**: 541-547; 2004

SOCIAL/PUBLIC HEALTH II

- Human papillomavirus (HPV) / cervical neoplasia
- Difference in median time to clear HPV infection



MOLECULAR DETECTION RATES

STI Agent	Percentage Detection from Females	
	Initial Validation (n = 1086)	Community Audit (n = 7277)
<i>Chlamydia trachomatis</i>	9.5	5.7
<i>Neisseria gonorrhoeae</i>	6.1	1.4
<i>Trichomonas vaginalis</i>	14.5	9.3

J. Clin. Microbiol. **46**: 3368-3374; 2008

J. Clin. Microbiol. **49**: 4190-4194; 2011

OTHER *T. vaginalis* DETECTION

Modality	Performance Indices (%)		
	Sensitivity	Specificity	Reference
Wet mount microscopy	48.1	99.8	1
	47.1	100.0	2
Antigen detection	78-84	99-100	3
	35.1	99.9	4
Nucleic acid hybridization	63.4	99.9	5

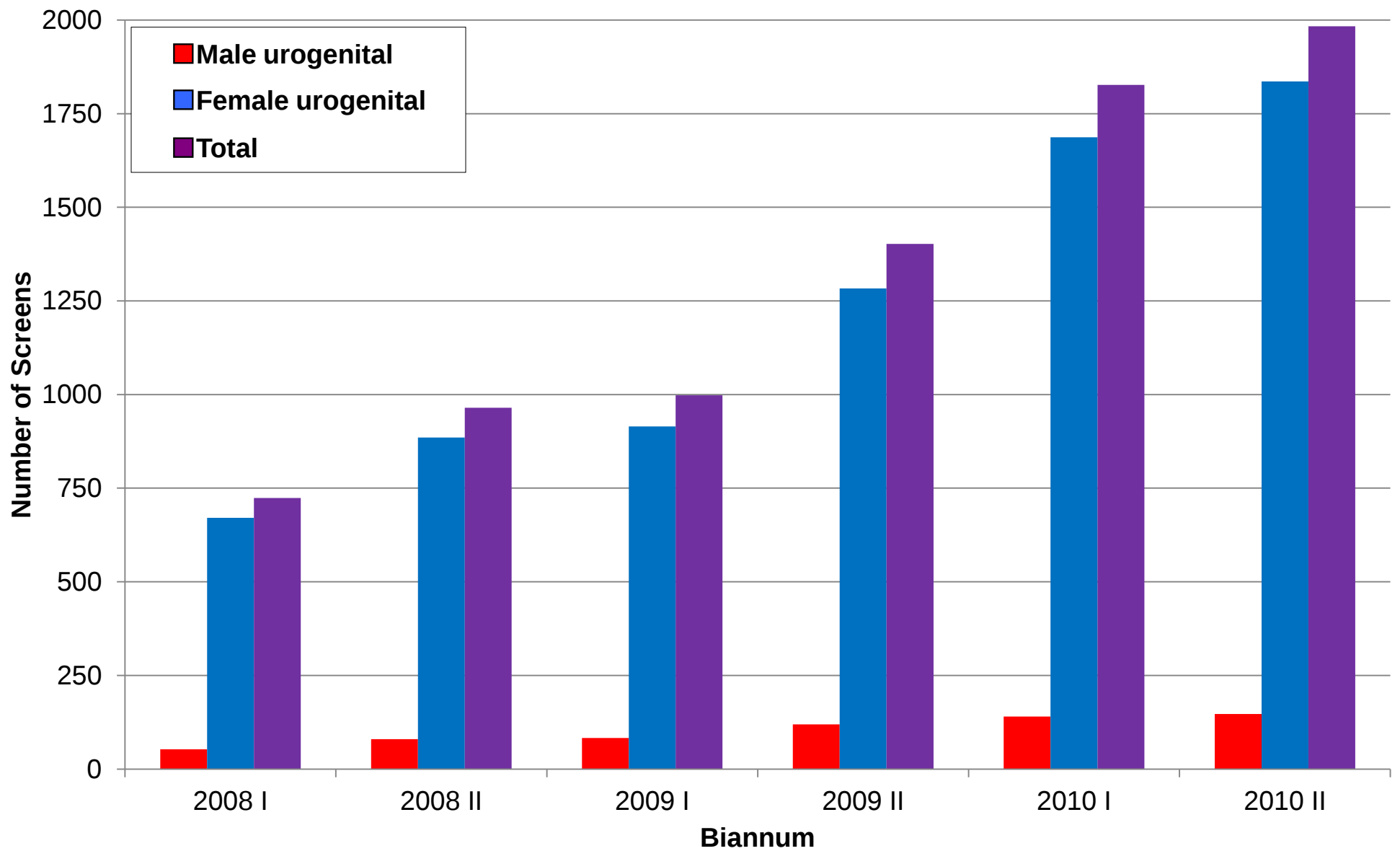
¹J. Clin. Microbiol. **46**: 3368-3374; 2008

²Diagn. Microbiol. Infect. Dis. **68**: 66-72; 2010

³Sex. Transm. Infect. **86**: 514-519; 2010

⁴J. Clin. Microbiol. PMID 26659216

⁵J. Clin. Microbiol. **49**: 4190-4194; 2011



ORDERING PRACTICES

Testing Modality	Percentage of Female Genital Swabs		
	2004-2007	2008-2010	<i>P</i> value
Any wet mount preparation	66.2	57.7	< 0.0002
Point-of-care wet mount preparation	27.8	22.4	< 0.0002
Any assessment for <i>Trichomonas vaginalis</i>	66.2	83.6	< 0.0002
<i>Chlamydia trachomatis</i> / <i>Neisseria gonorrhoeae</i> TMA	80.4	83.7	< 0.0002

DETECTION RATE

Specimen	Percentage Detection		
	<i>Trichomonas vaginalis</i>	<i>Chlamydia trachomatis</i>	<i>Neisseria gonorrhoeae</i>
Endocervix	8.9	5.7	1.3
Vagina	8.6	4.8	0.4
Female urine	12.6	6.0	2.6

DETECTION RATE

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Endocervix	8.9	5.7	1.3
Vagina	8.6	4.8	0.4
Female urine	12.6	6.0	2.6

$P = 0.85$

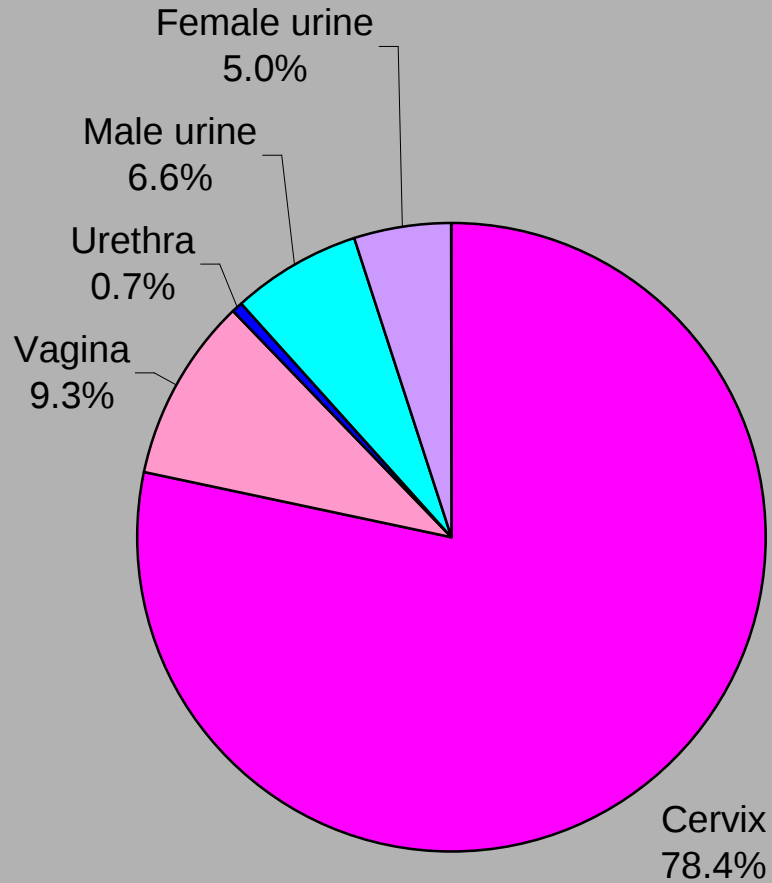
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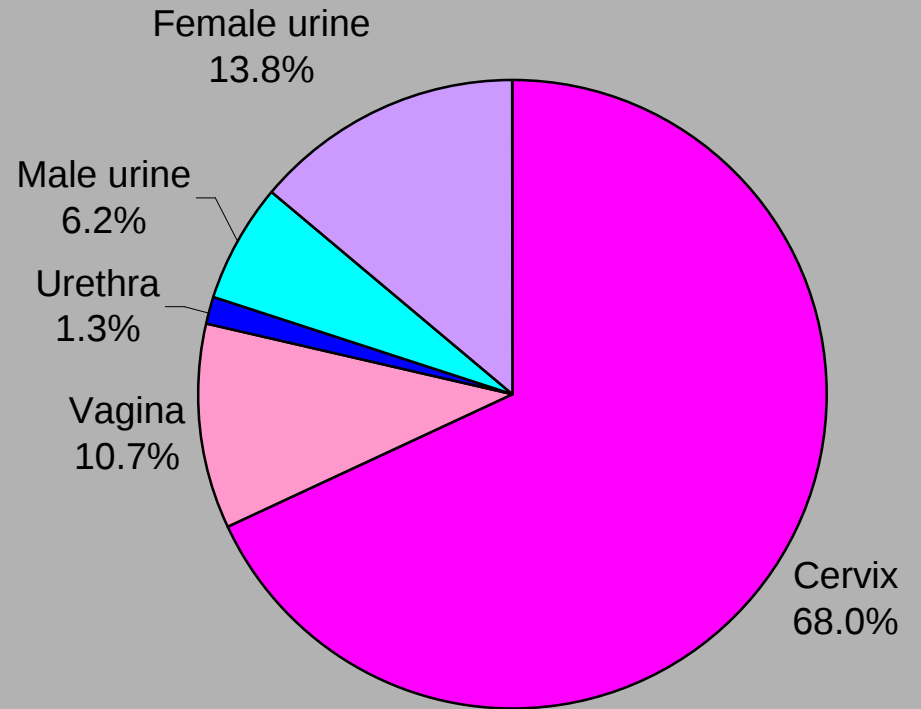
$P = 0.85$

$P < 0.0004$

2008 I

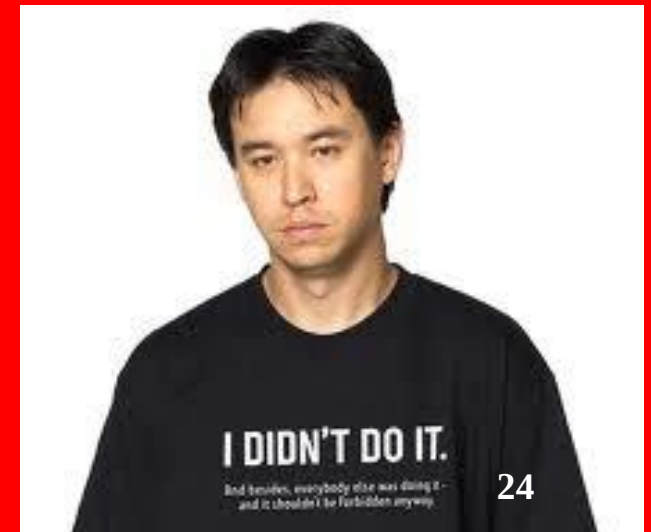


2010 II





Testing of Males for *T. vaginalis*



CLINICAL/PUBLIC HEALTH

- Non-gonococcal urethritis; persistent, scant, mucoid discharge; prostatitis

Sex. Transm. Dis. 7: 135-136; 1980

J. Chemother. 14: 537-538; 2002

- Complications include infertility, hypogonadism

J. Clin. Microbiol. 13: 880-881; 1981

- HIV transmission

<u>Clinical condition</u>	<u>Median copies HIV RNA/mL semen</u>
<i>T. vaginalis</i> urethritis	3.45×10^5
Non- <i>T. vaginalis</i> urethritis	0.05×10^5

Sex. Transm. Dis. 26: 381-387; 1999

POPULATION STUDIES/PROSTATE

- 13% of prostate cancer pts. with *T. vaginalis* Ab
9% of age-matched controls with *T. vaginalis* Ab

Cancer Epidemiol. Biomarkers Prev. **15**: 939-945; 2006

- 0.97 odds ratio for prostate cancer in men with
T. vaginalis seropositivity

Int. J. Cancer. **124**: 2082-2087; 2009

- 1.25 odds ratio for prostate cancer in physicians
with *T. vaginalis* seropositivity

J. Natl. Cancer. Inst. **101**: 1406-1411; 2009

INCREASED CARCINOGENICITY?

- Increased risk of advanced-stage prostate cancer diagnosis in men with positive *T. vaginalis* serostatus

Cancer Epidemiol. Biomarkers Prev. **15**: 939-945; 2006

- Odds ratio of 6.4 (95% CI 1.5-27.9) for diagnosis of lethal prostate cancer in seropositive patients with documented history of *T. vaginalis* infection

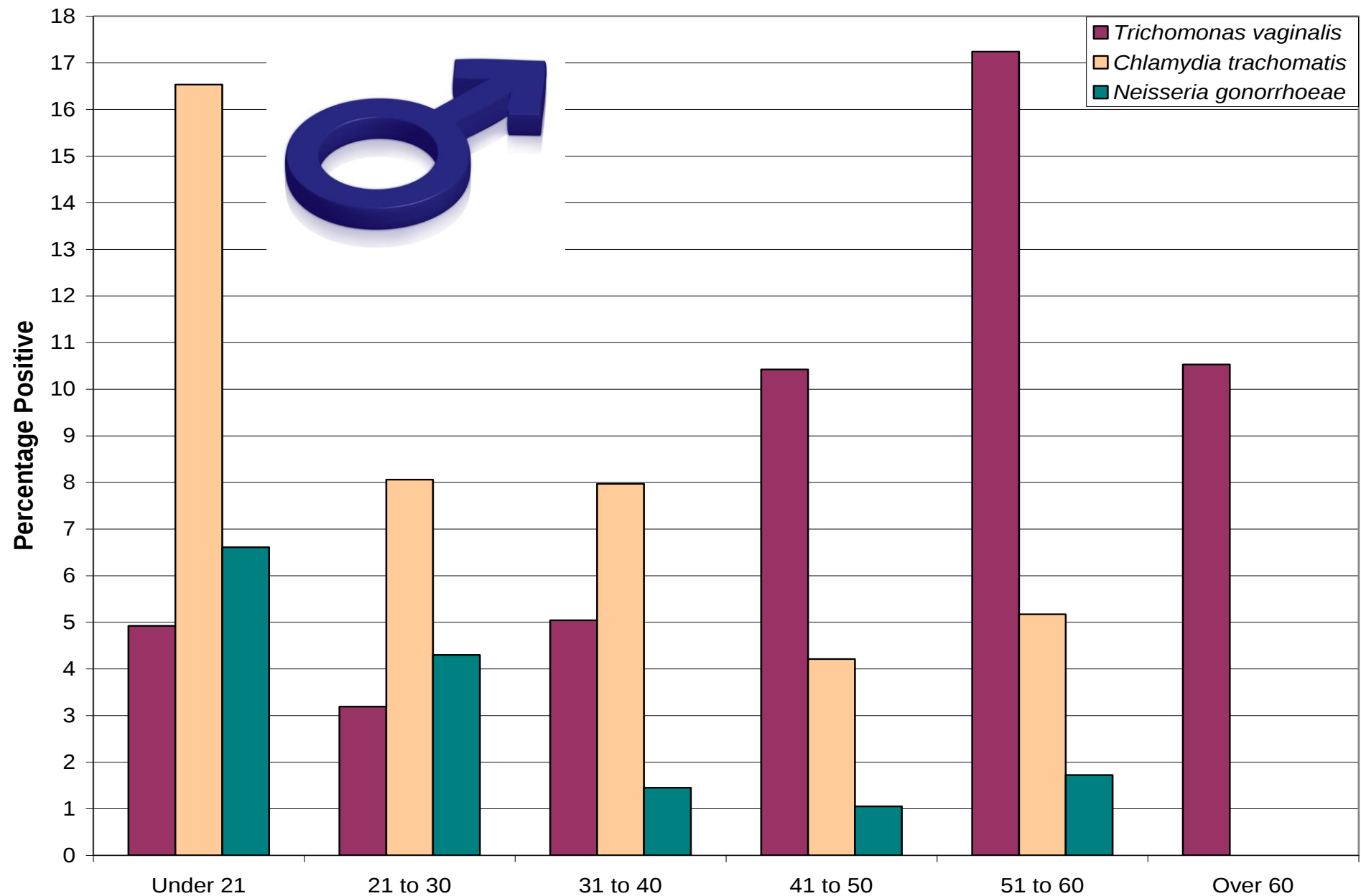
J. Natl. Cancer. Inst. **101**: 1406-1411; 2009

- Prostate carcinogenesis mechanism undefined

PLoS Pathog. **8**: e1002801; 2012

EVOLVING REFERENCE STANDARD

Diagnostic method and specimen	Number of specimens				Sensitivity		Specificity		Predictive value (%)	
	True positive	False positive	False negative	True negative	%	95% CI	%	95% CI	Positive	Negative
Infected patient status algorithm										
Culture	12	0	0	286	100	69.9-100	100	98.3-100	100	100
PCR - Urethral swab	11	13	1	273	91.7	59.8-99.6	95.5	92.2-97.5	45.8	99.6
PCR - Urine	11	9	1	277	91.7	59.8-99.6	96.9	93.9-98.5	55.0	99.6
ATV - Urethral swab	11	38	1	248	91.7	59.8-99.6	86.7	82.1-90.3	22.5	99.6
ATV - Urine	11	23	1	263	91.7	59.8-99.6	91.9	88.0-94.7	32.1	99.6
Molecular resolved algorithm										
Culture	12	0	30	256	28.6	16.2-44.8	100	98.2-100	100	89.4
PCR - Urethral swab	23	0	19	256	54.8	38.8-69.8	100	98.2-100	100	93.1
PCR - Urine	20	0	22	256	47.6	32.3-63.4	100	98.2-100	100	92.0
ATV - Urethral swab	40	9	2	247	95.2	82.6-99.2	96.5	93.2-98.3	81.7	99.2
ATV - Urine	31	4	11	252	73.8	57.7-85.6	98.4	95.8-99.5	88.6	95.8



race

The 10 most segregated urban areas in America

Slide show: The new census numbers provide a sobering reminder of how separate white and black America still are

BY DANIEL DENVIR

American Indian	Asian	Black	Hispanic	White
50.0% or less	50.0% or less	50.0% or less	50.0% or less	50.0% or less
50.1 to 85.0%	50.1 to 85.0%	50.1 to 85.0%	50.1 to 85.0%	50.1 to 85.0%
85.1% or more	85.1% or more	85.1% or more	85.1% or more	85.1% or more

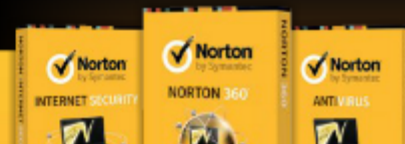
JOHN PAUL DEWITT OF CENSUSSCOPE.ORG AND THE UNIVERSITY OF MICHIGAN'S SOCIAL SCIENCE DATA ANALYSIS NETWORK

No. 1: Milwaukee

Main city population: 594,833
Metropolitan population: 1,555,908
Segregation level (dissimilarity): 81.52

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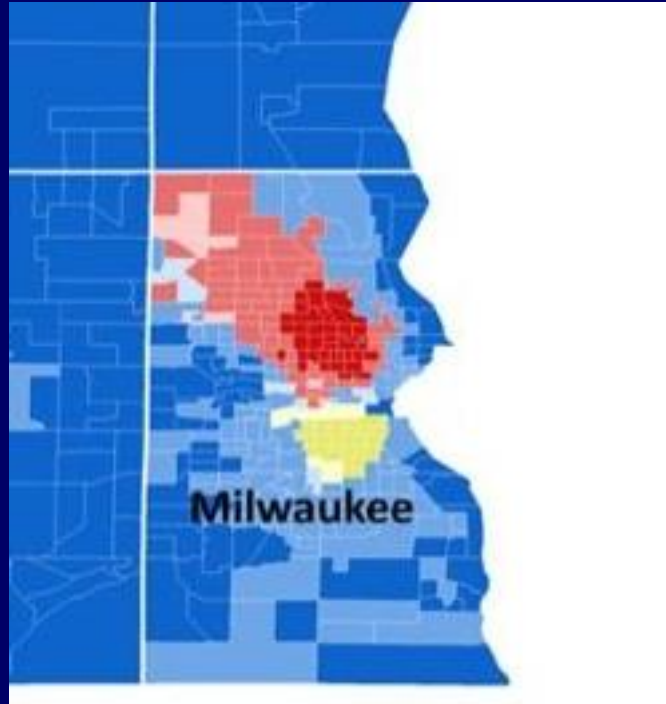
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11 MILWAUKEE COUNTY ZIP CODES



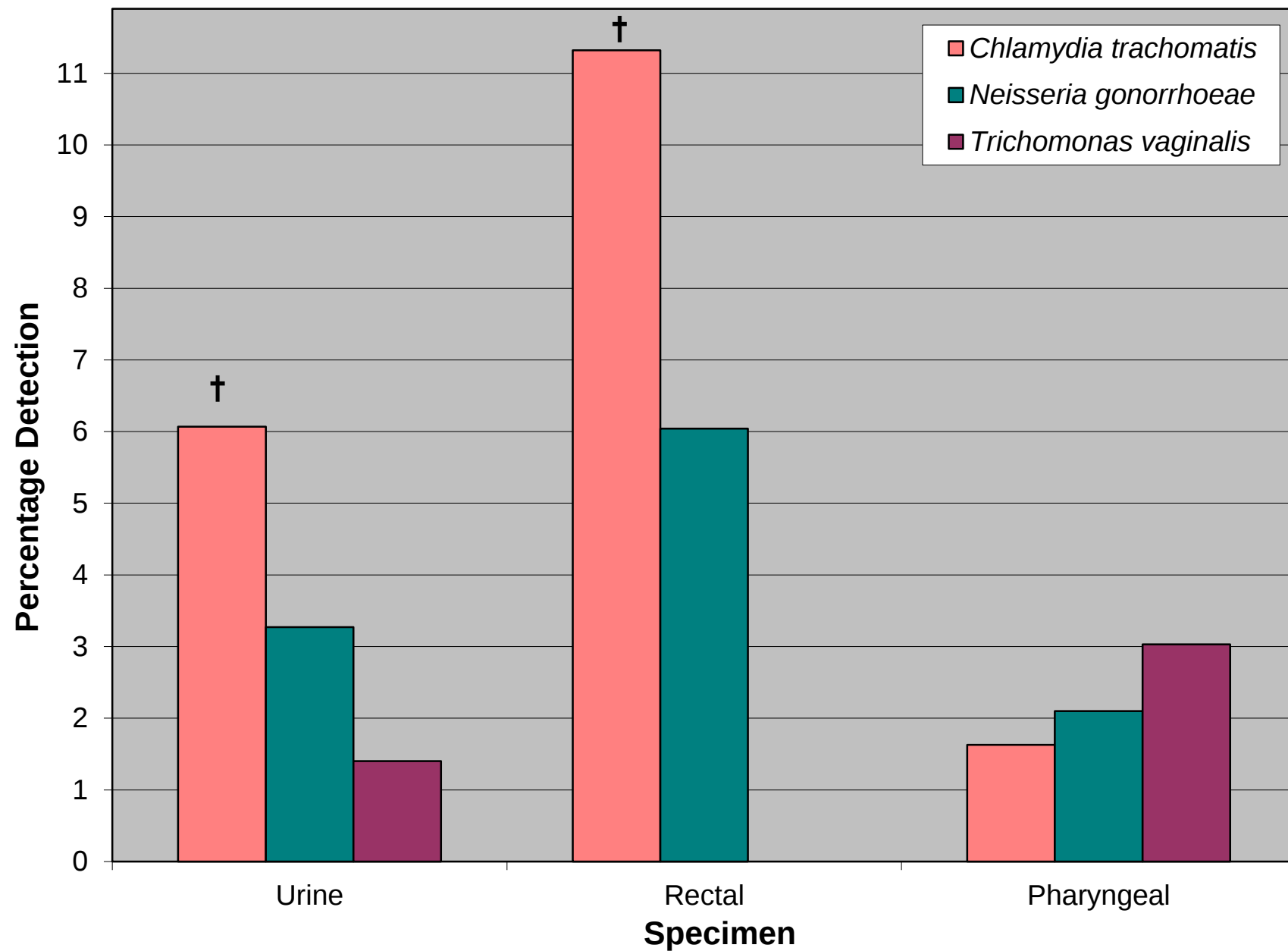
African American (7): Mean difference between African American and Caucasian populations was 43.9% per ZIP

Caucasian (4): Mean difference between Caucasian and African American populations was 32.6% per ZIP

RACE/ETHNICITY (Males)

Parameter	Geographical Region Race Majority		
	African American	Caucasian	<i>P</i> value
Percentage urine submissions	78.4	72.3	0.16
Mean screenings per ZIP code	49.7	34.8	0.26
Percentage detection of:			
<i>Trichomonas vaginalis</i>	8.9	5.0	0.15
<i>Chlamydia trachomatis</i>	8.4	9.4	0.74
<i>Neisseria gonorrhoeae</i>	3.7	4.3	0.78





Mycoplasma genitalium



Int. J. Syst. Bacteriol. **33**: 387-396; 1983

CLINICAL SIGNIFICANCE (MALES)

- Increased *M. genitalium* molecular detection in males with acute non-gonococcal urethritis (NGU) than in males without NGU

J. Eur. Acad. Dermatol. Venerol. **18**: 1-11; 2004

- *M. genitalium*-positive males more likely to exhibit urethritis than *C. trachomatis*-positive males

Sex. Transm. Infect. **80**: 289-293; 2004

- Male infertility; spermatozoa motility

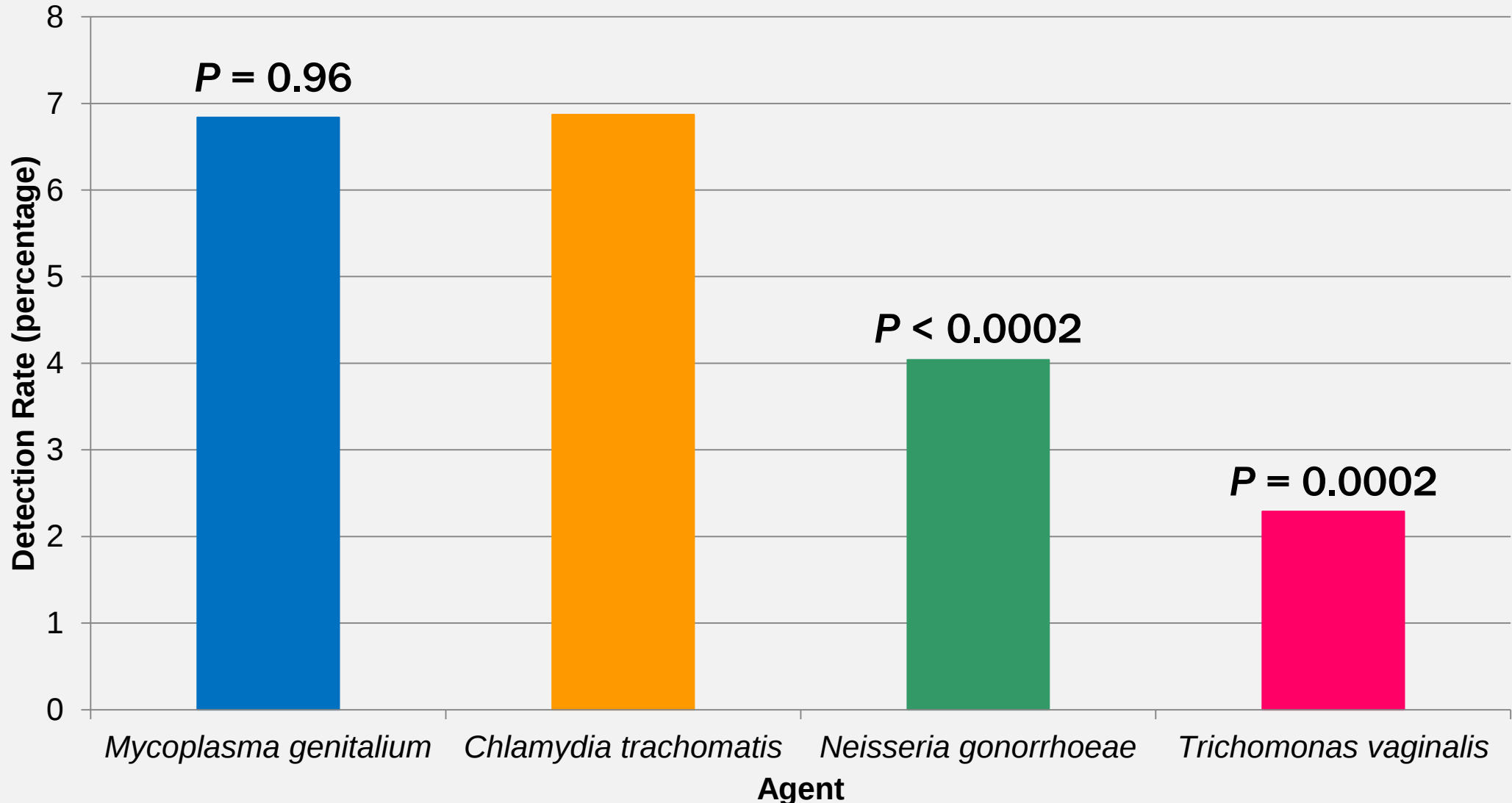
Clin. Microbiol. Rev. **24**: 498-514; 2011



ASSESSMENT OF MALES

- Prospective sampling of 2750 residual urines via *M. genitalium* research-use only TMA
- Previous TMA testing: *Chlamydia trachomatis*
Neisseria gonorrhoeae
Trichomonas vaginalis
- Source of specimens
Outpatient clinics (community setting)
Milwaukee STI clinic (demographics, history available)

DETECTION RATE (MALES)



AGE OF POSITIVE MALES

Agent	Median	Mean	Range
<i>Mycoplasma genitalium</i>	29	30.81	14-74
<i>Chlamydia trachomatis</i>	26	27.80	15-64
<i>Neisseria gonorrhoeae</i>	29	31.14	15-66
<i>Trichomonas vaginalis</i>	42	41.60	16-85

All mean detection age comparison $P \leq 0.006$, except *N. gonorrhoeae* vs. *M. genitalium* ($P = 0.78$)

STI CLINIC; *M. genitalium* ONLY

- Preferences 58.9% heterosexual
 8.4% bisexual
 32.6% homosexual
- Partners median 4
 mean 5.18
 range 1-30
- 60.6% symptomatic for urogenital disease
 - Discharge 49.1% Dysuria 14.0%
 - Burning/tingling 35.1% Itching 14.0%

STI Phenotype				Percentage of Patients Delineated by Healthcare Setting		
<i>M. genitalium</i>	<i>Chlamydia</i>	<i>Neisseria</i>	<i>Trichomonas</i>	STI Clinic	Outpatient	<i>P</i> value
+	-	-	-	36.5	22.0	0.0007
+	+	-	-	6.4	4.8	0.45
+	-	+	-	3.4	1.0	0.08
-	+	-	-	25.9	32.1	0.14
-	+	+	-	3.8	6.2	0.22
-	-	+	-	16.5	12.4	0.21
-	-	-	+	5.3	18.7	< 0.0002
Any detection of <i>Mycoplasma genitalium</i>				47.4	29.7	0.0002
Any detection of <i>Chlamydia trachomatis</i>				36.5	44.0	0.10
Any detection of <i>Neisseria gonorrhoeae</i>				25.6	20.6	0.20
Any detection of <i>Trichomonas vaginalis</i>				7.1	21.1	< 0.0002

CLINICAL SIGNIFICANCE (FEMALES)

- Females with high-burden *M. genitalium* more likely to shed HIV-1 DNA than *M. genitalium*-negative females

J. Infect. Dis. **197**: 733-736; 2008

- Associated w/ reproductive disease (meta-analysis)

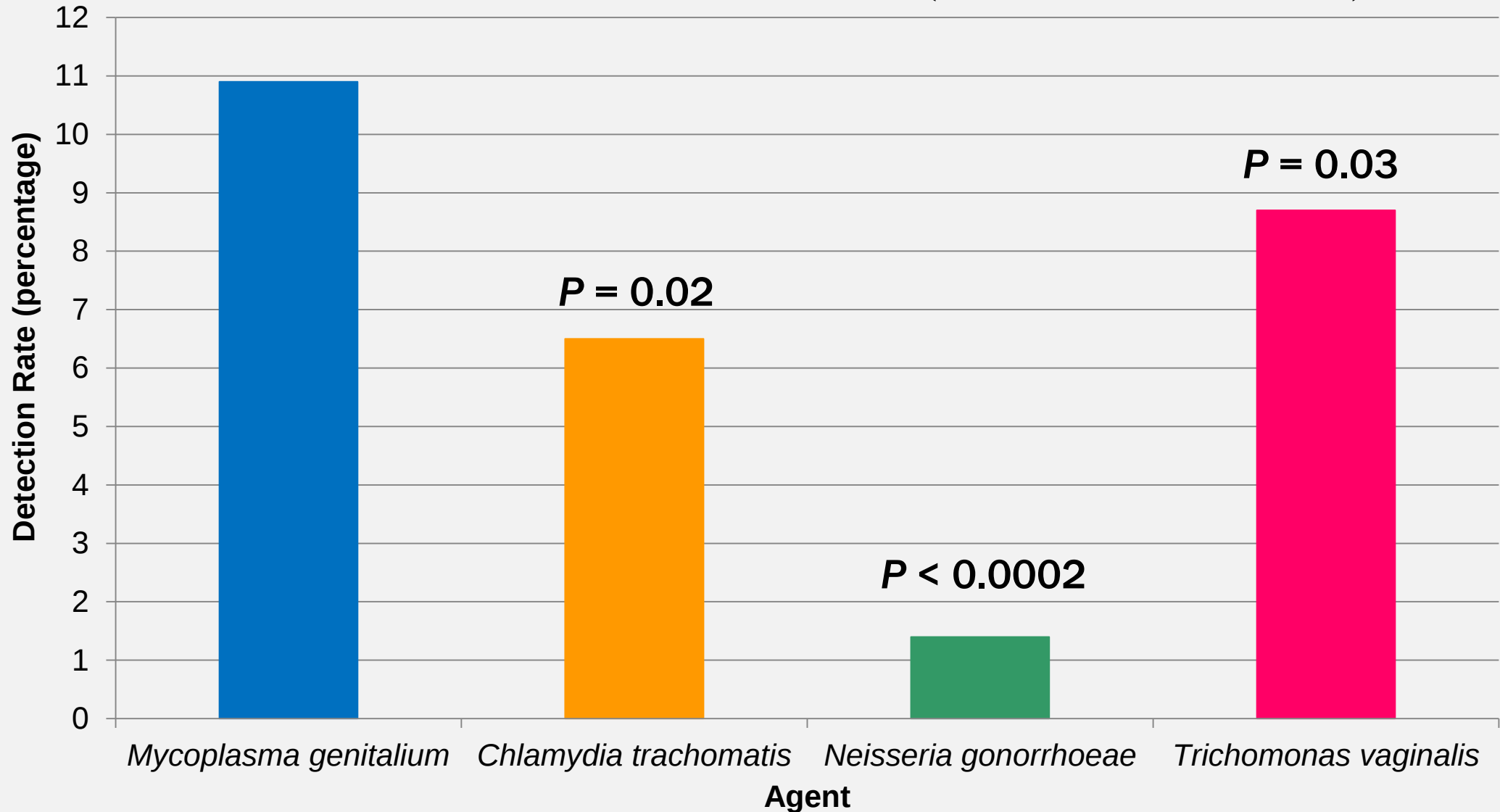
Cervicitis	pooled OR 1.65
PID	pooled OR 2.53
Pre-term birth	pooled OR 2.33
Spontaneous abortion	pooled OR 1.82

Clin. Infect. Dis. **61**: 418-426; 2015

ASSESSMENT OF FEMALES

- Retrospective/random selection of 2478 urine, cervical, or vaginal specimens via *M. genitalium* research-use only TMA
- Previous TMA testing: *Chlamydia trachomatis*
Neisseria gonorrhoeae
Trichomonas vaginalis
- Assessment of study set via comparison to 6-month audit of routine *C. trachomatis* TMA
age, location, detection rate, specimen source

DETECTION RATE (FEMALES)



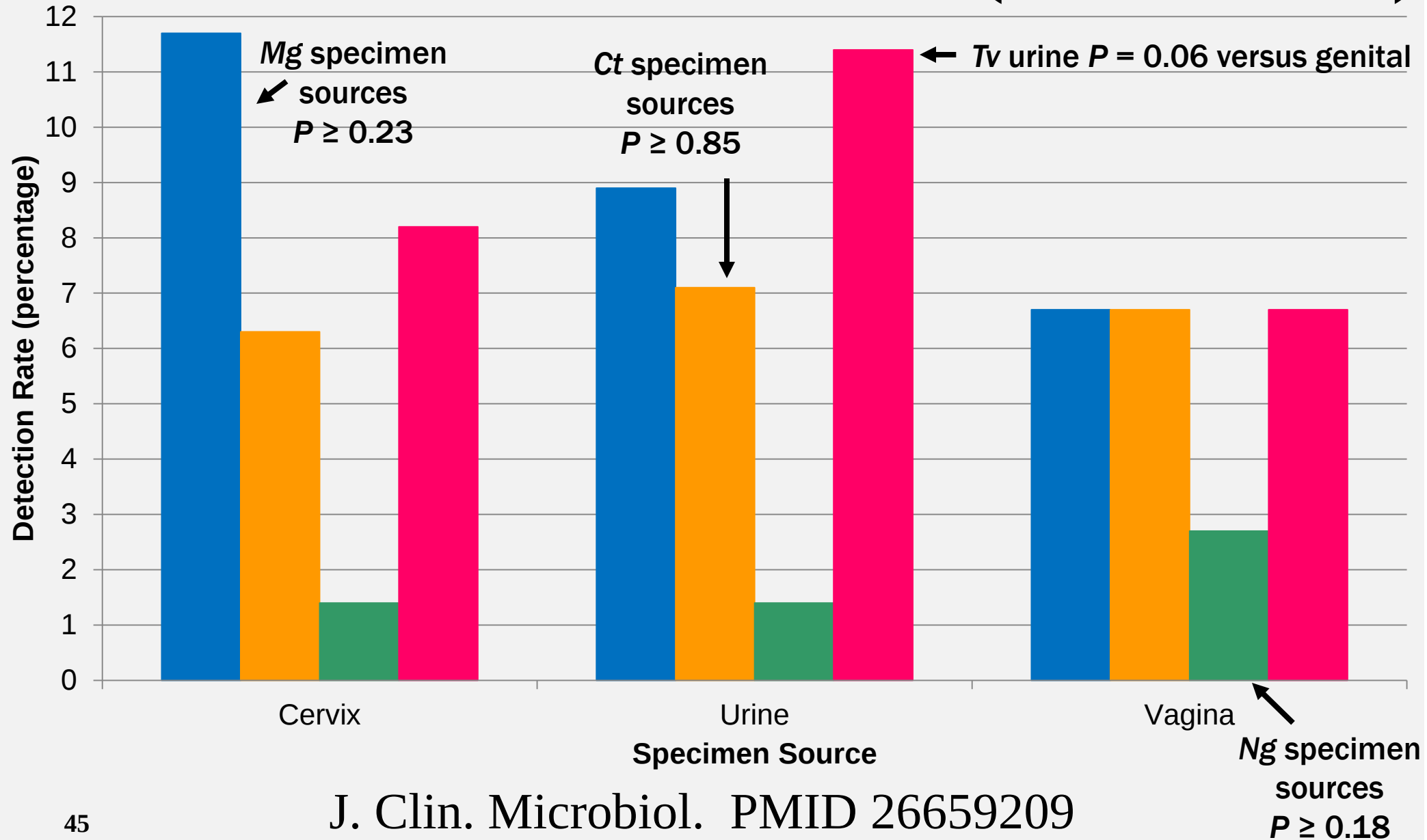
AGE OF POSITIVE FEMALES

Agent	Median	Mean	Range
<i>Mycoplasma genitalium</i>	23	24.74	14-65
<i>Chlamydia trachomatis</i>	21	22.75	14-54
<i>Neisseria gonorrhoeae</i>	21	23.47	15-46
<i>Trichomonas vaginalis</i>	28	30.09	15-68

Mean *M. genitalium*, *N. gonorrhoeae* ages $P = 0.30$

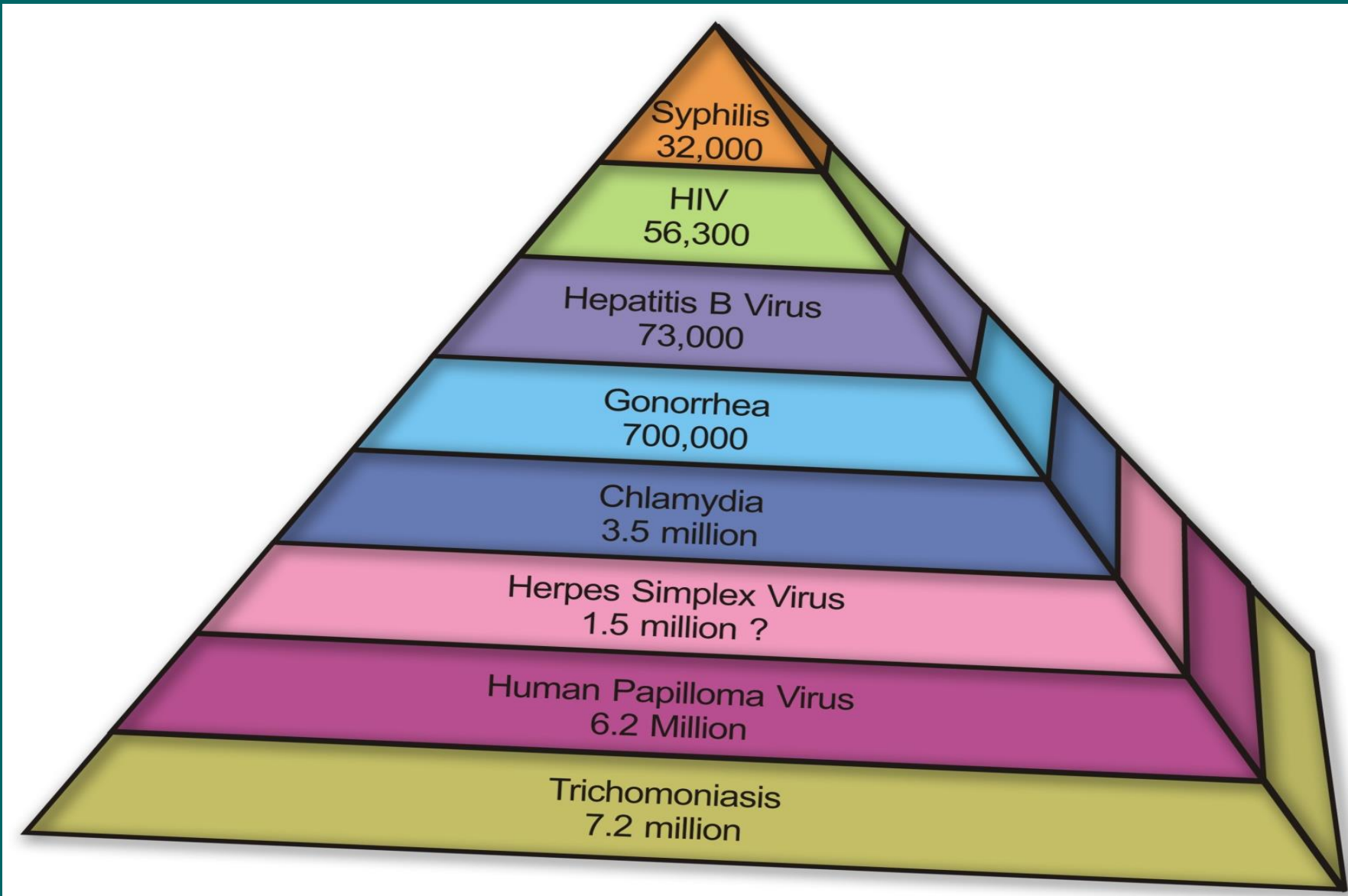
Mean *C. trachomatis*, *N. gonorrhoeae* ages $P = 0.56$

DETECTION BY SOURCE (FEMALES)



EMERGENT VERSUS “SUBACUTE”

Setting	n	<i>M. genitalium</i> detection (%)	<i>T. vaginalis</i> detection (%)	<i>P</i> value
Emergency Department	755	14.6	13.0	0.37
Non-Emergency Department	1723	10.0	7.2	0.004



Courtesy of Charlotte Gaydos, Dr.Ph. (via Fred Jones, Ph.D.)

HPV AND CANCER

- 90% of cervical cancers caused by HPV

Int. J. Cancer. **52**: 743-749; 1992

- High-risk HPV types:

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

Obstet. Gynecol. **79**: 328-337; 1992

EVOLUTION OF HPV DIAGNOSTICS

Chemistry	Product	Manufacturer	Mechanism
Hybrid capture	H _c 2	Digene (Qiagen)	DNA hybridization
Invader [®]	Cervista [™]	Third Wave (Hologic)	DNA hybridization
PCR	Cobas [®] 4800	Roche	DNA amplification
TMA	APTIMA HPV	Gen-Probe (Hologic)	RNA transcription

Comparison of Three Management Strategies for Patients With Atypical Squamous Cells of Undetermined Significance: Baseline Results From a Randomized Trial

Diane Solomon, Mark Schiffman, Robert Tarone

For the ALTS Group

Background: More than 2 million U.S. women receive an equivocal cervical cytologic diagnosis (atypical squamous cells of undetermined significance [ASCUS]) each year. Effective colposcopy triage strategies are needed to identify the minority of women who have clinically significant disease while avoiding excessive follow-up evaluation for others. **Methods:** The ASCUS/LSIL (i.e., low-grade squamous intraepithelial lesion) Triage Study (ALTS) is a multicenter, randomized trial comparing the sensitivity and specificity of the following three management strategies to detect cervical intraepithelial neoplasia grade 3 (CIN3): 1) immediate colposcopy (considered to be the reference standard), 2) triage to colposcopy based on human papillomavirus (HPV) results from Hybrid Capture 2™ (HC 2) and thin-layer cytology results, or 3) triage based on cytology results alone. This article summarizes the cross-sectional enrollment results for 3488 women with a referral diagnosis of ASCUS. All statistical tests are two-sided. **Results:** Among participants with ASCUS, the underlying prevalence of histologically confirmed CIN3 was 5.1%. Sensitivity to detect CIN3 or above by testing for cancer-associated HPV DNA was 96.3% (95% confidence interval [CI] = 91.6% to 98.8%), with 56.1% of women referred to colposcopy. Sensitivity of a single repeat cytology specimen with a triage threshold of HSIL or above was 44.1% (95% CI = 35.6% to 52.9%), with 6.9% referred. Sensitivity of a lower cytology triage threshold of ASCUS or above was 85.3% (95% CI = 78.2% to 90.8%), with 58.6% referred. **Conclusions:** HC 2 testing for cancer-associated HPV DNA is a viable option in the management of women with ASCUS. It has greater sensitivity to detect CIN3 or above and specificity comparable to a single additional cytologic test indicating ASCUS or above. [J Natl Cancer Inst 2001;93:293-9]

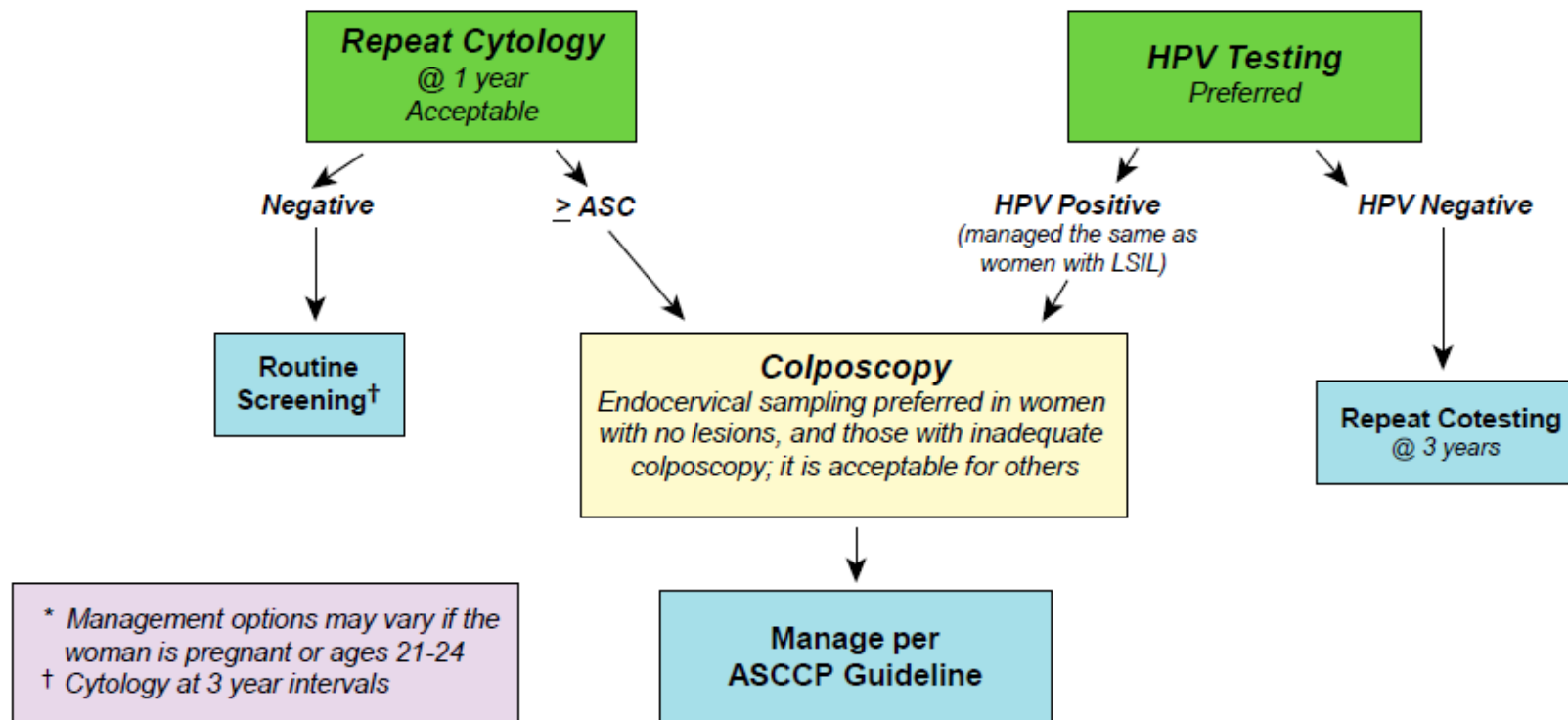
J. Natl. Cancer Inst.
93: 293-299; 2001

ALTS

Use molecular
testing to triage
ASC-US patients

Test Performance	H_c2	
Participants	5000	
Mean Age	29	
Colposcopies	1149	
% with no lesion (no biopsy)	25	
% with no pathology upon biopsy	49	
% CIN1	15	
% CIN2+	11	
Detection of CIN2+ (%) via HPV DNA	96	
Detection of CIN3+ (%) via HPV DNA	96	
Negative predictive value for CIN2+ (%)	98.9	
Negative predictive value for CIN3+ (%)	99.5	
Referral to colposcopy (%)	57	
PCR concordance (%)	82.7	

Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology*



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CERVISTA EVALUATION

Cytologic Classification	Percentage Detection		<i>P</i> value
	Cervista™	H _c 2	
HSIL	90.0	90.0	1.00
LSIL	57.1	78.6	0.22
ASC-US	36.4	42.9	0.18
NILM	11.8	12.6	0.82
Total	30.2	35.2	0.17

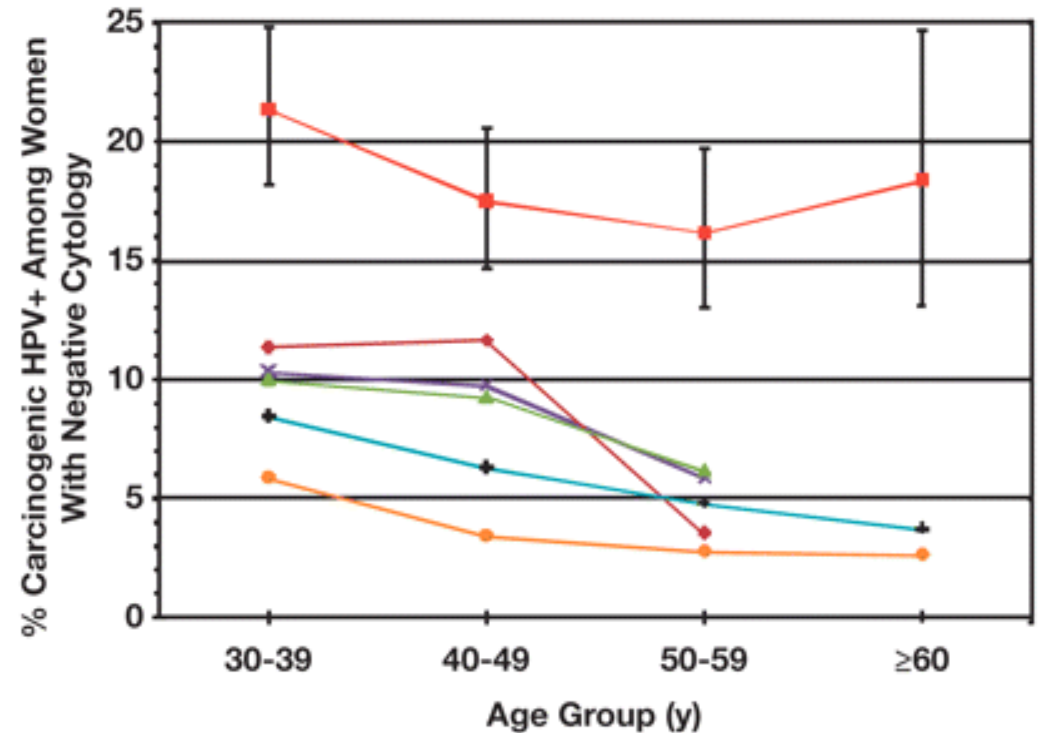
Test Performance	H_c2	Cervista™
Participants	5000	~3500
Mean Age	29	33
Colposcopies	1149	1347
% with no lesion (no biopsy)	25	28
% with no pathology upon biopsy	49	53
% CIN1	15	14
% CIN2+	11	5
Detection of CIN2+ (%) via HPV DNA	96	93
Detection of CIN3+ (%) via HPV DNA	96	100
Negative predictive value for CIN2+ (%)	98.9	99.1
Negative predictive value for CIN3+ (%)	99.5	100.0
Referral to colposcopy (%)	57	57
PCR concordance (%)	82.7	86.1

CERVISTA “TOO POSITIVE”??

Special Commentary

Patient Safety and the Next Generation of HPV DNA Tests

Walter Kinney, MD,¹ Mark H. Stoler, MD,² and Philip E. Castle, PhD, MPH³



SUMMARY OF METHODS

- 2386 ThinPrep vials for H_c2 performance at reference laboratory during nine months of 2008-2009
- 2380 ThinPrep vials for Cervista™ performance in-house during nine months of 2009-2010

FREQUENCY OF DIAGNOSIS

Cytologic Classification	Percentage Diagnosis		<i>P</i> value
	Cervista™ arm	H _c 2 arm	
HSIL	0.4	0.8	0.13
LSIL	2.4	1.8	0.17
ASC-US	22.8	16.7	<0.0002
NILM	73.7	80.2	<0.0002

RETROSPECTIVE COMPARISON

Cytologic Classification	Percentage Detection		<i>P</i> value
	Cervista™	H _c 2	
HSIL	70.0	72.2	0.90
LSIL	79.3	79.5	0.98
ASC-US	40.3	43.0	0.41
NILM	9.1	7.7	0.14

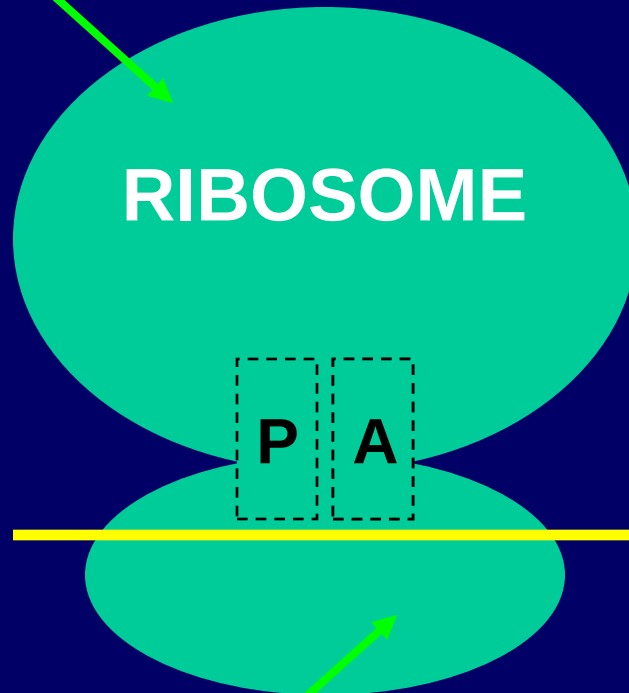
RETROSPECTIVE COMPARISON

Cytologic Classification	Percentage Detection		<i>P</i> value
	Cervista™	H _c 2	
ASC-US; age < 30	54.1	61.3	0.24
ASC-US; age ≥ 30	29.0	30.6	0.77
NILM; age < 30	16.2	21.8	0.42
NILM; age ≥ 30	8.9	7.0	0.10

TRANSCRIPTION

Evidence of bioactivity
Evidence of persistence

50S subunit



RIBOSOME

P A

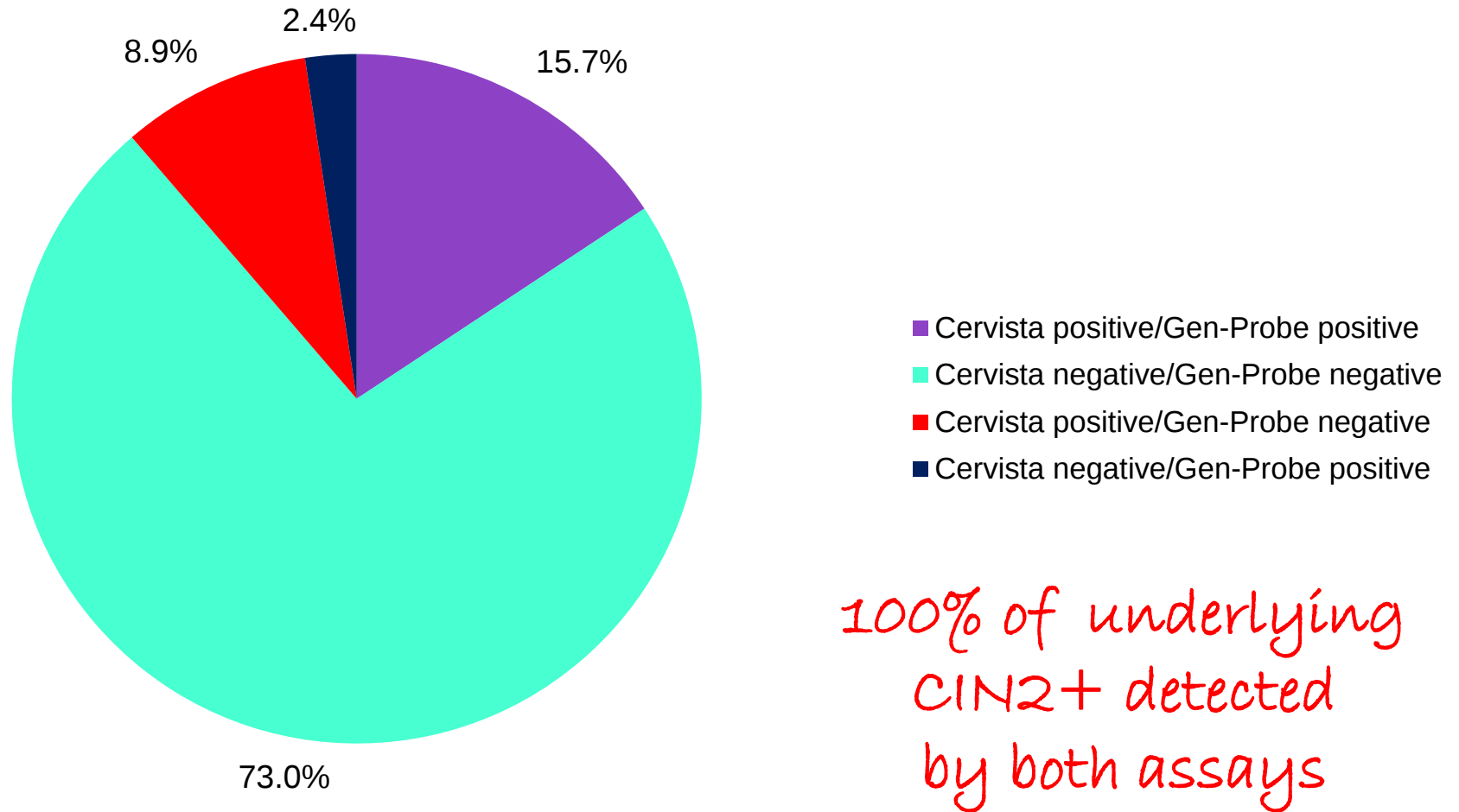
messenger RNA

30S subunit

A NEW PARADIGM

- Detection of E6/E7 (RNA) transcripts from high-risk HPV
- Potential to ascribe (precursory) oncogenic function to HPV nucleic acid detected in ThinPrep specimens

PROSPECTIVE COMPARISON



HPV PCR

- 226 ThinPrep vials subjected to Cervista™; also HPV PCR via Cobas® 4800
- 25.7% concordant positive
56.7% concordant negative
2.7% Cervista™ negative; Cobas® positive
15.0% Cervista™ positive; Cobas® negative

ADJUDICATION

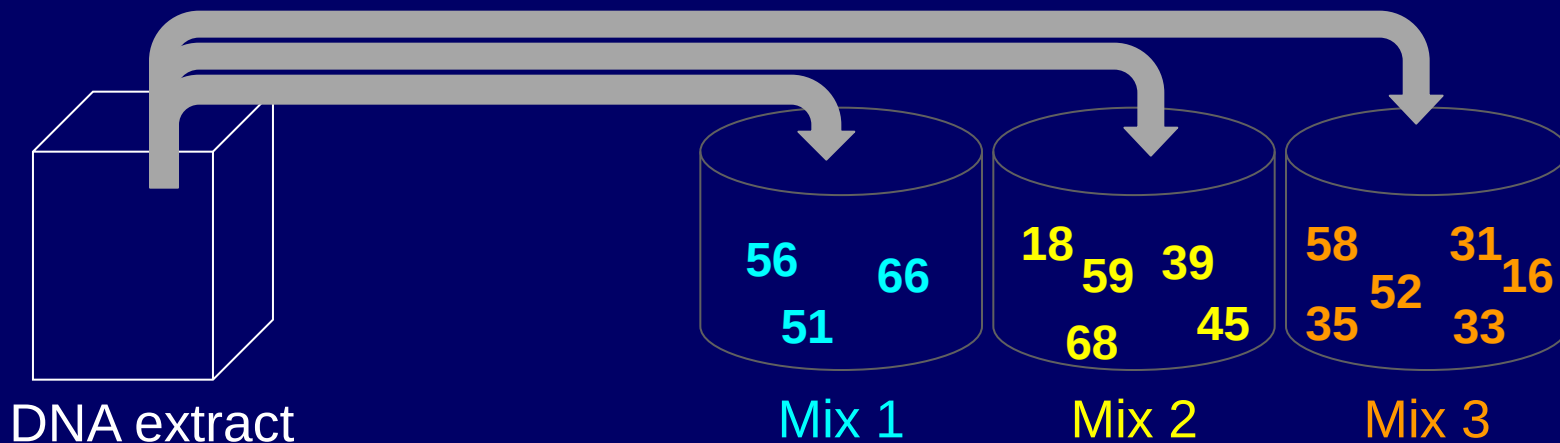
Of 5 COBAS® 4800 negative/
Cervista positive specimens,
HPV sequencing revealed 3 low-risk HPV
and 2 HPV-negative results

RETROSPECTIVE COMPARISON

Cytologic Classification	Percentage Detection		<i>P</i> value
	Cervista™	Gen-Probe HPV	
HSIL	94.7	100.0	0.31
ASC-H	80.0	80.0	1.00
LSIL	78.7	73.8	0.98
ASC-US	49.3	43.9	0.02
NILM	13.7	6.6	< 0.0002
Cumulative	24.5	18.0	< 0.0002

CERVISTA POSITIVES

- Pool of 14 high-risk HPV oligonucleotides distributed among three mixes

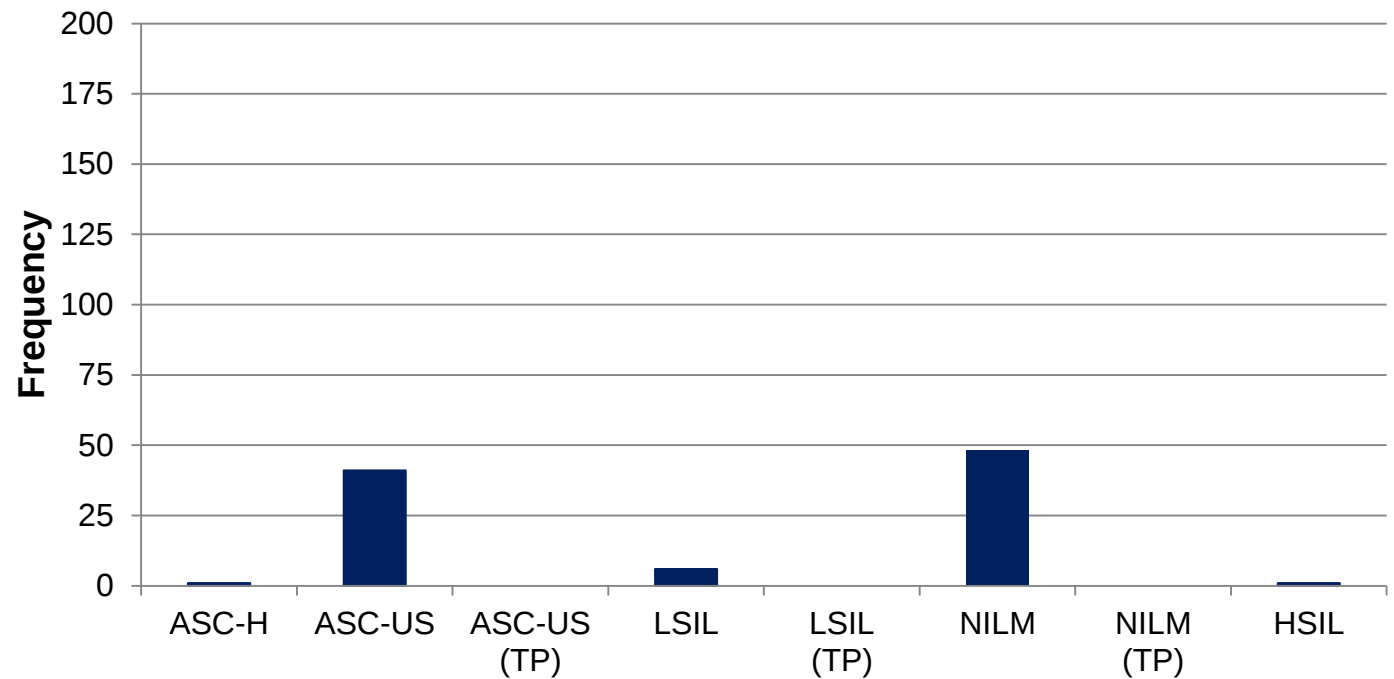


- Hybridization signal versus background:

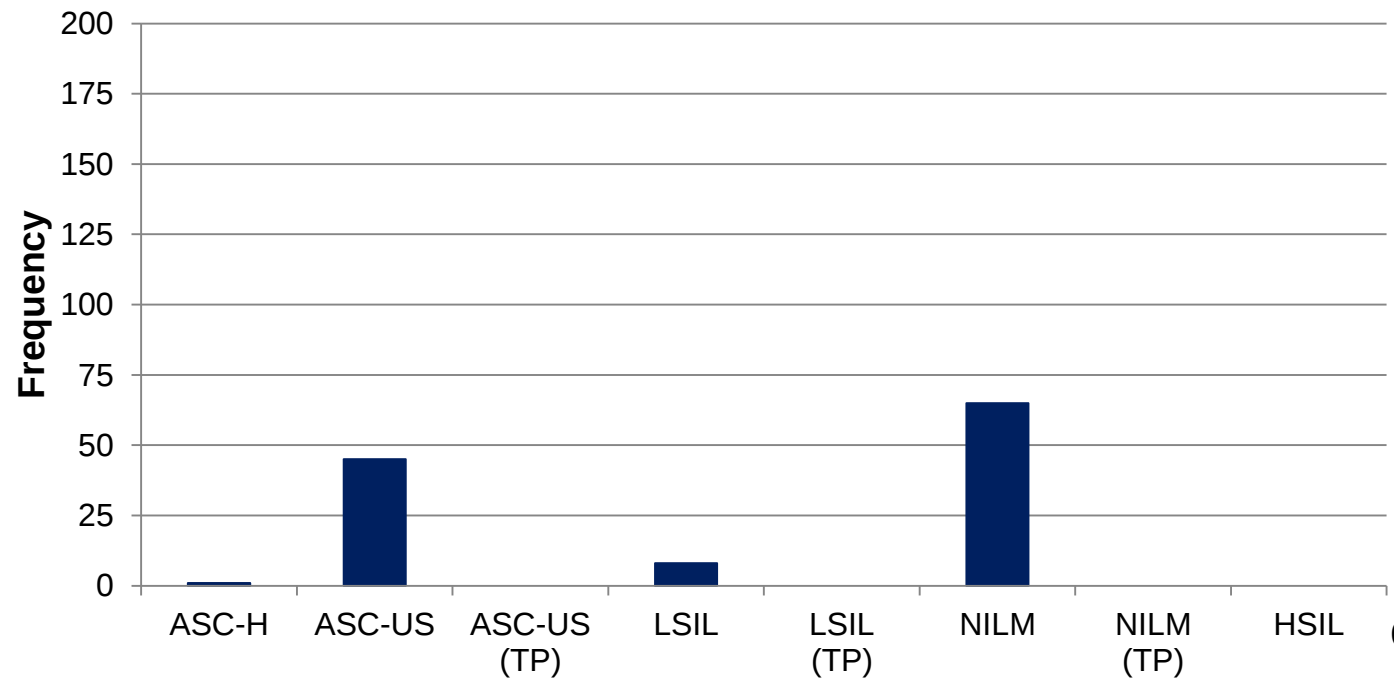
Positive if one or two mixes exceeds 1.525

Positive if all three exceed 1.92 (**triple-positive; TP**)

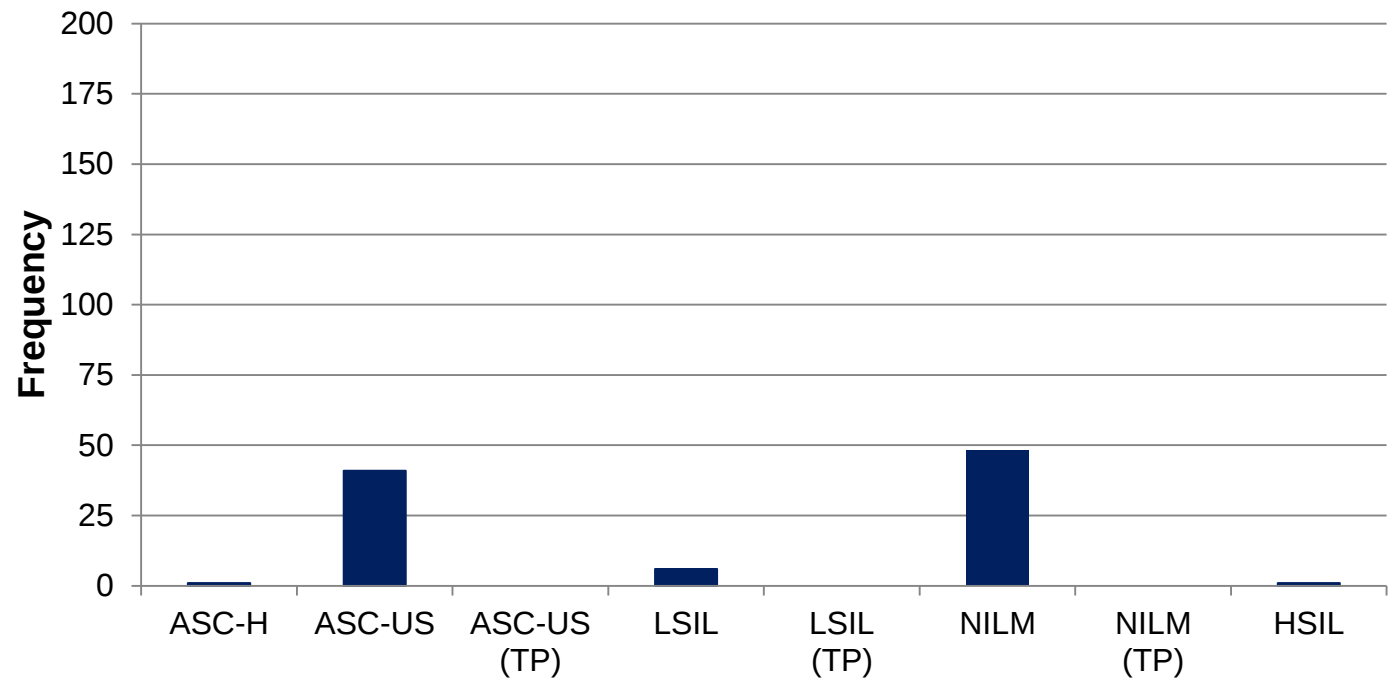
*Cervista negative/
Gen-Probe positive*



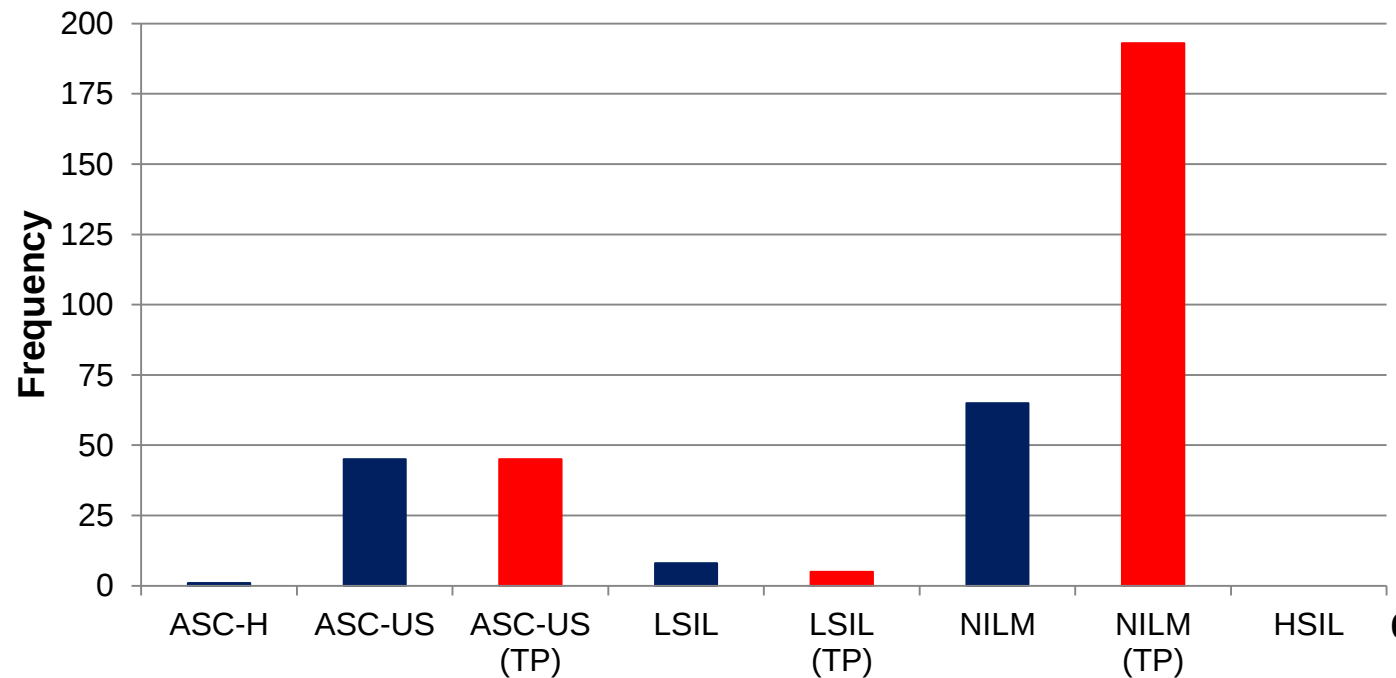
*Cervista positive/
Gen-Probe negative*



*Cervista negative/
Gen-Probe positive*



*Cervista positive/
Gen-Probe negative*



RELATIVE LUMINESCENT OUTPUT

Gen-Probe Result	n	Mean Cervista™ Luminescence from: ^a			
		Mix 1 ^b	Mix 2 ^b	Mix 3 ^b	Genomic DNA
positive	19	5.69	5.02	5.44	17.58
negative	244	3.29 ^c	2.61 ^c	3.14 ^c	19.40 ^d

^aFrom Cervista™ TP specimens

^bTP hybridization signal versus background exceeds 1.92 for all three mixes

^c $P < 0.0001$ versus mean luminescence from Gen-Probe positive specimens

^d $P = 0.05$ versus mean luminescence from Gen-Probe positive specimens

BASIS FOR GENOTYPING

- HPV high-risk types 16, 18, 45 most associated with cervical cancer

75% of squamous cell carcinoma

94% of adenocarcinoma

- Co-detection of high-risk types 18, 45 more common in adenocarcinoma (44%) than squamous cell carcinoma (14%)

BASIS FOR GENOTYPING

- Mean age of patients with cervical cancer

Type 45:	46.8	Type 16:	50.0
Type 18:	48.2	Other types:	56.0

Lancet Oncol. **11**: 1048-1056; 2011

- Integration frequency
predictive of quicker
progression to
invasive cancer

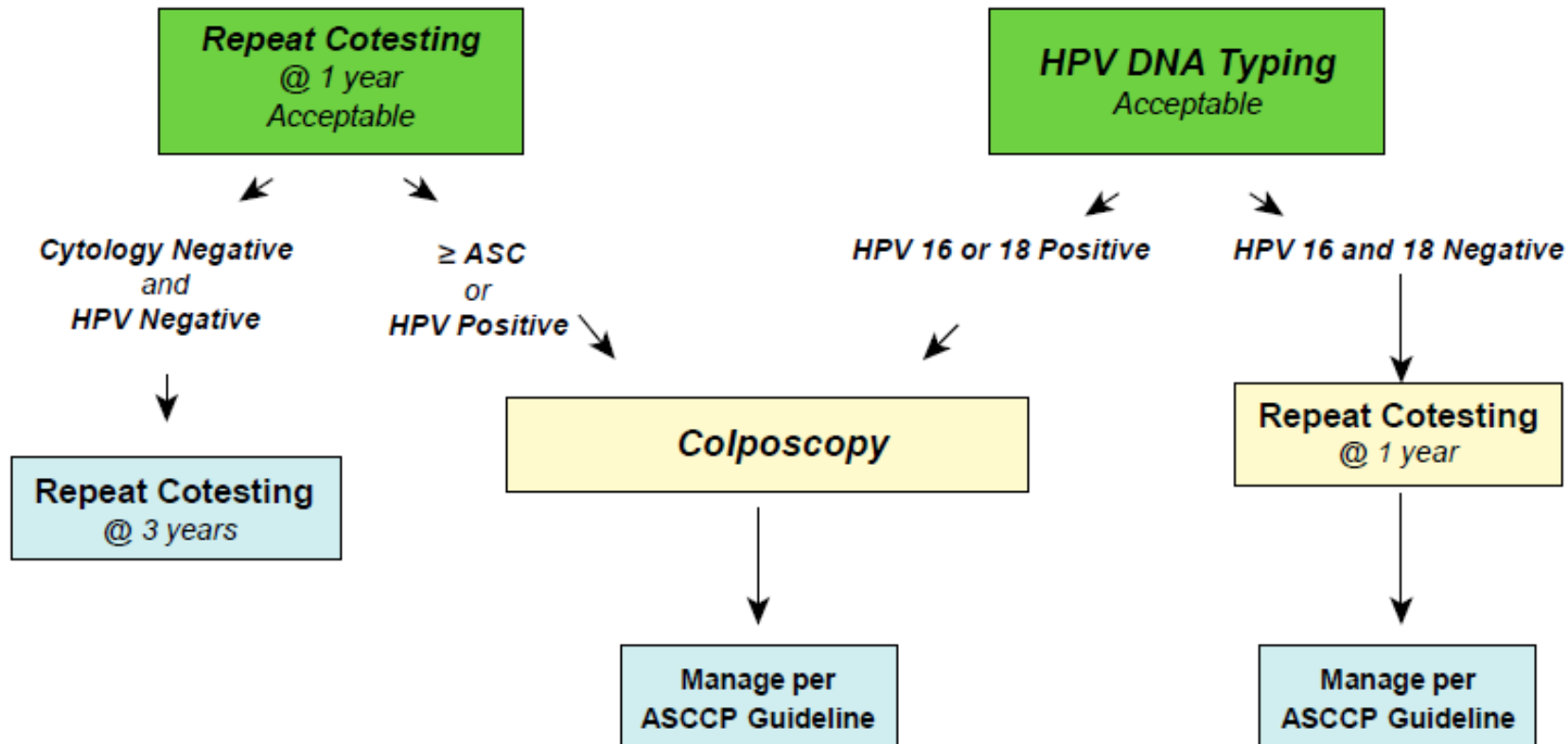
Type 18:	92-100%
Type 45	83%
Type 16:	55-80%
Type 33:	37%
Type 31:	14%

J. Med. Virol. **67**: 574-582; 2002

J. Pathol. **212**: 356-367; 2007

Cancer Res. **68**: 307-313; 2008

Management of Women $\geq$ Age 30, who are Cytology Negative, but HPV Positive



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GEN-PROBE GENOTYPING

Cytologic Classification	Percentage Positive HPV High-risk 16 ^a	
	< 30 years	≥ 30 years
NILM ^b	7.9	12.7
Non-NILM ^c	19.7	19.6

Cytologic Classification	Percentage Positive HPV High-risk 18/45 ^a	
	< 30 years	≥ 30 years
NILM ^b	8.9	10.4
Non-NILM ^c	10.6	15.6

^aDataset derived from HPV high-risk screen-positive specimens

^b745 total NILM specimens

^c816 total non-NILM specimens

SUMMARY

- Changing epidemiology of trichomoniasis on basis of highly-accurate molecular assay
- *M. genitalium* dichotomy within females and males on basis of novel molecular assay
- Cervista™ and Gen-Probe HPV acceptable triage performance; Gen-Probe HPV specificity
- Benefits for HPV 16, 18/45 genotyping