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Recommendations for the Laboratory-Based Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* — 2014

2014 CDC Guidelines Chlamydia & Gonorrhea Diagnostics

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Disclosures

- Honorarium, Speaking Fees or Research Support
  - Atlas Genetics
  - BD Diagnostics
  - Cepheid
  - Hologic
  - Melinta
  - Rheonix
  - Roche Molecular Diagnostics

Organization

- Why are we screening?
- How were the guidelines developed?
- What are the recommendations?
- How might the guidelines impact practice?

Things you Already Know

- Chlamydia & Gonorrhea are #1 and #2!
  - Chlamydia (~**1.4 million** cases in 2012)
  - Gonorrhea (~**333,000** cases)
  - Salmonella is 3rd with ~**58,000** cases
- Is high prevalence sufficient to warrant a national control plan?

WHY SCREEN

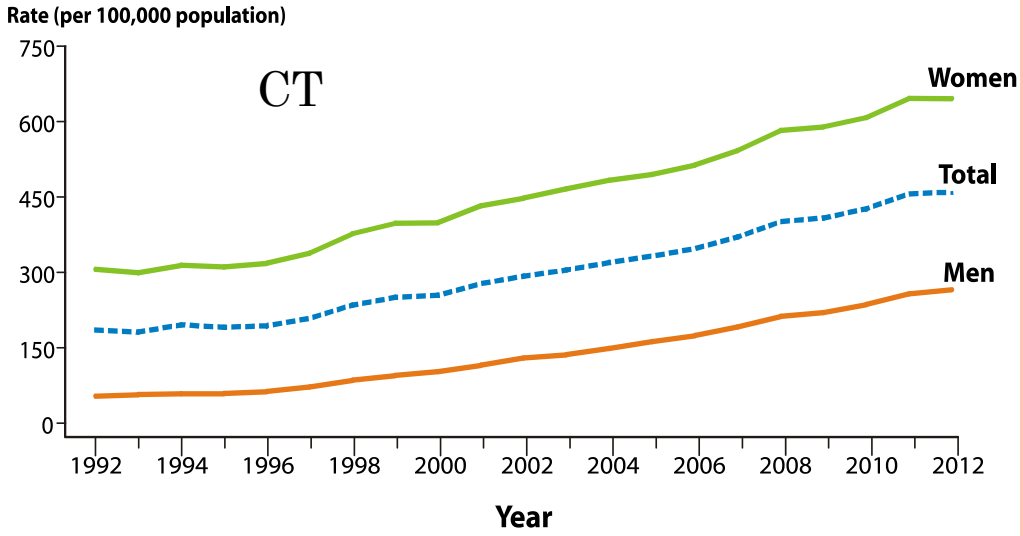
Frequency/Prevalence	***yes***
Severity	yes?
Health disparities	***yes***
Costs of negative outcomes	***yes***
Preventability	yes?
Communicability	yes
Public interest	yes?

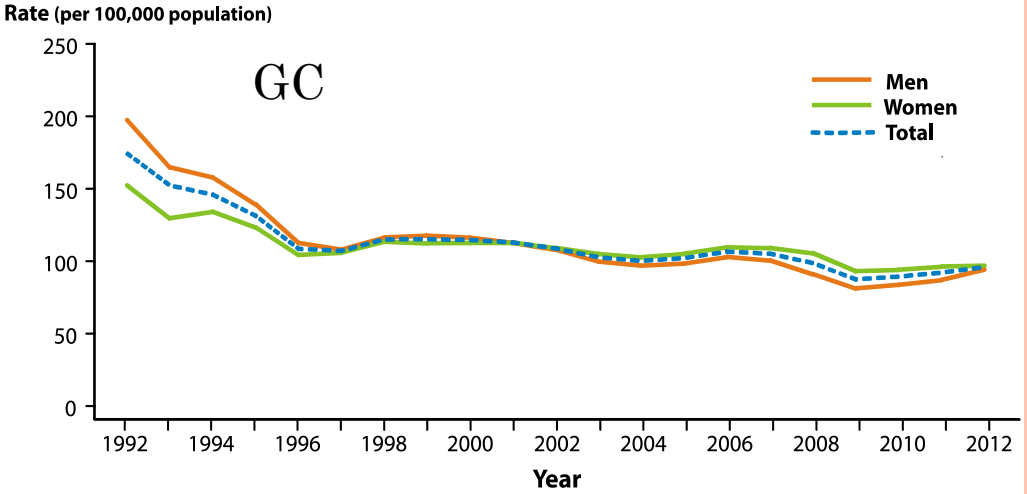
Adapted from Hoots et al, STD 40:113

Frequency/Prevalence

Rates are Increasing

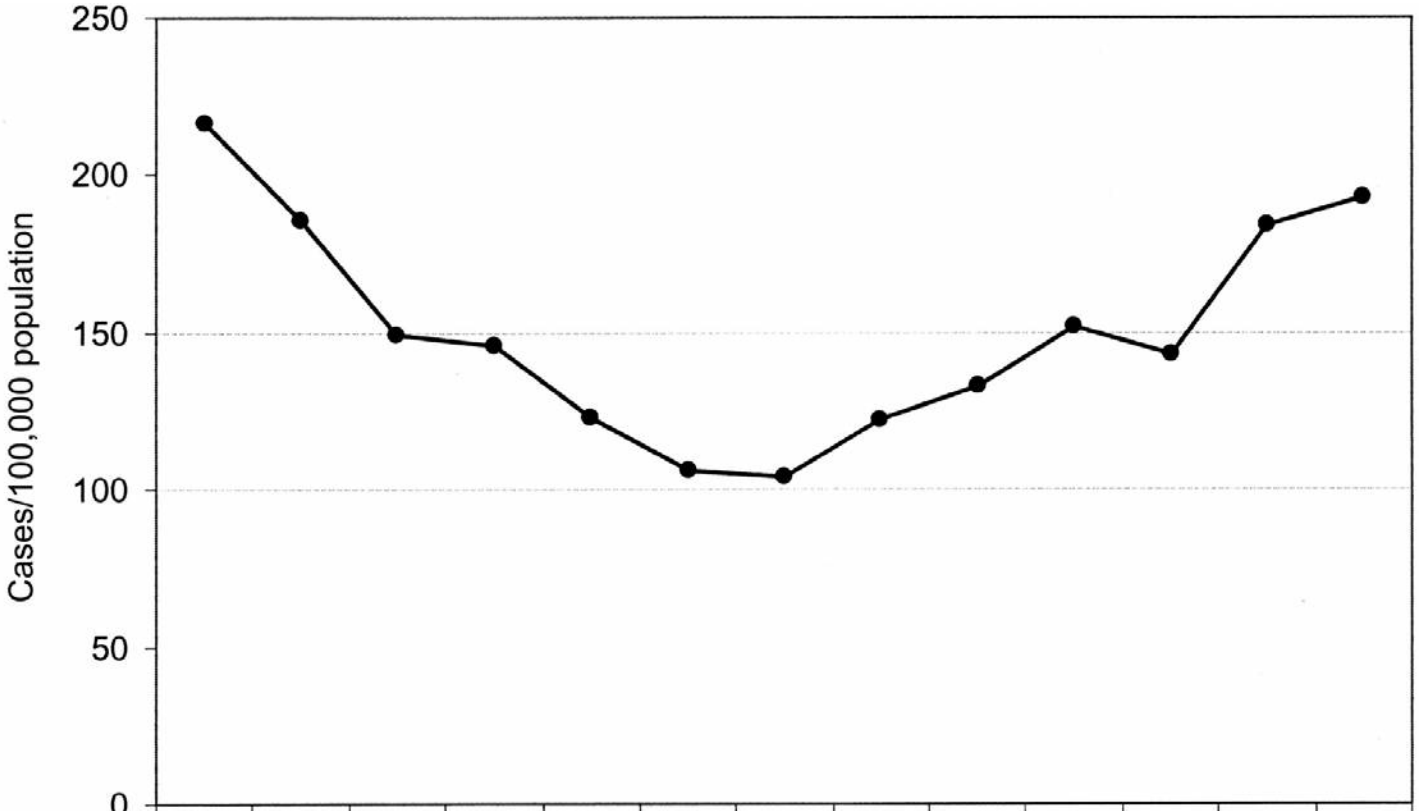
- Increased sensitivity of assays
- Increased testing
  - Poor denominator
- Actual increases





cdc.gov

Chlamydia trachomatis incidence rates in British Columbia from 1991 to 2003.

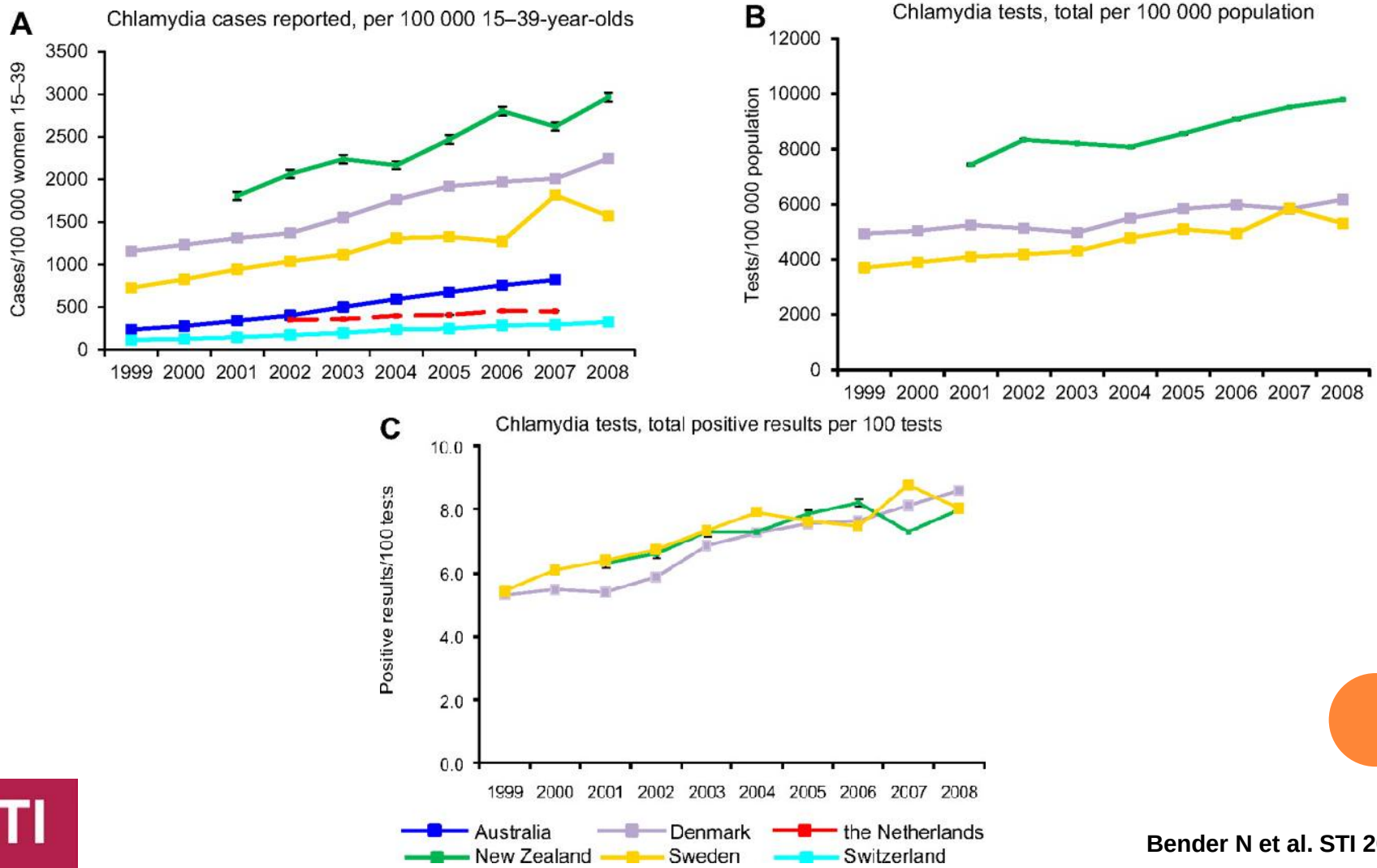


	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Cases	7294	6434	5321	5366	4660	4116	4116	4879	5356	6168	5871	7614	8050
Rate	216.2	185.4	149.0	145.7	123.1	106.0	103.9	122.1	133.0	151.9	143.1	183.9	192.6

The Journal of Infectious Diseases

Brunham R C et al. J Infect Dis. 2005;192:1836-1844

Trends in chlamydia diagnosis rates

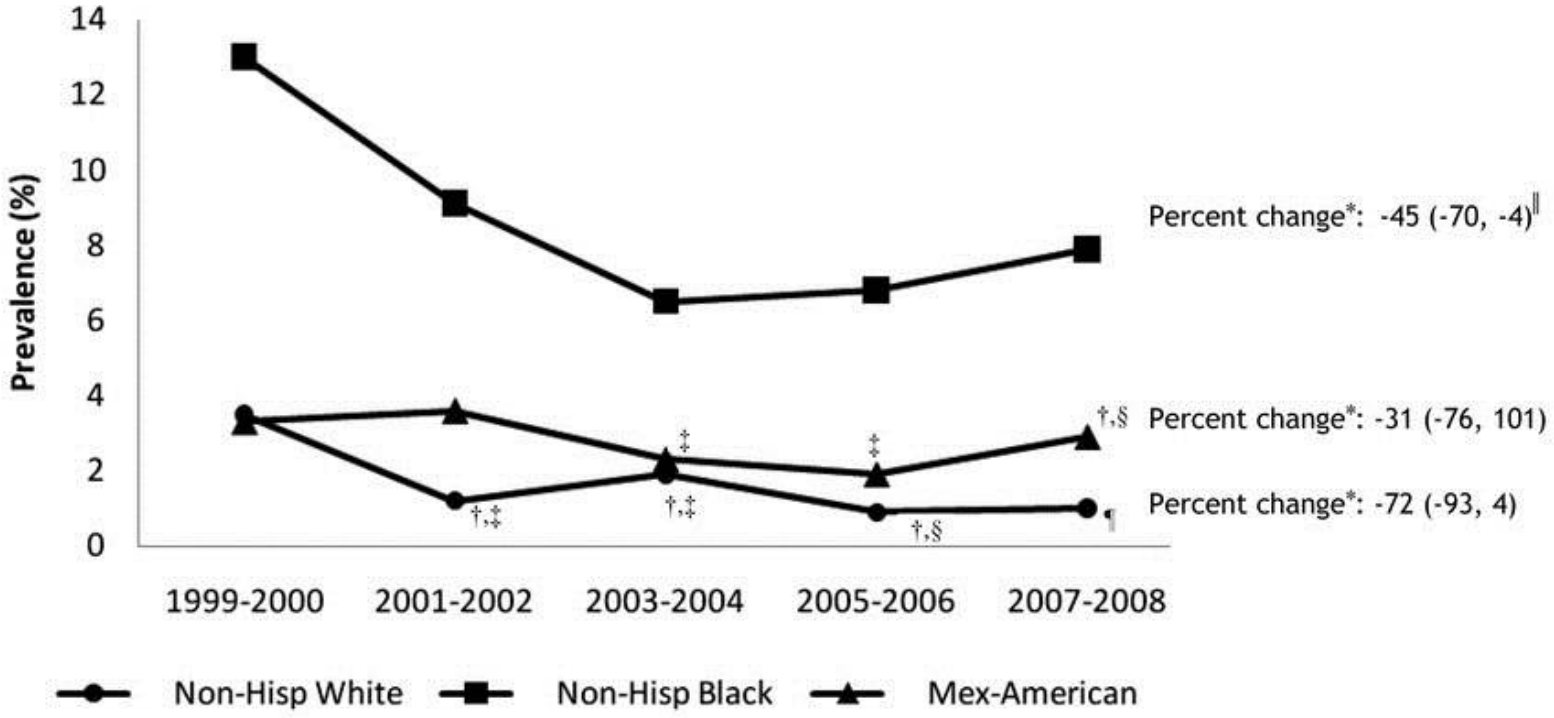


Bender N et al. STI 2011

STI

Health Disparities

Health Disparities [NHANES]

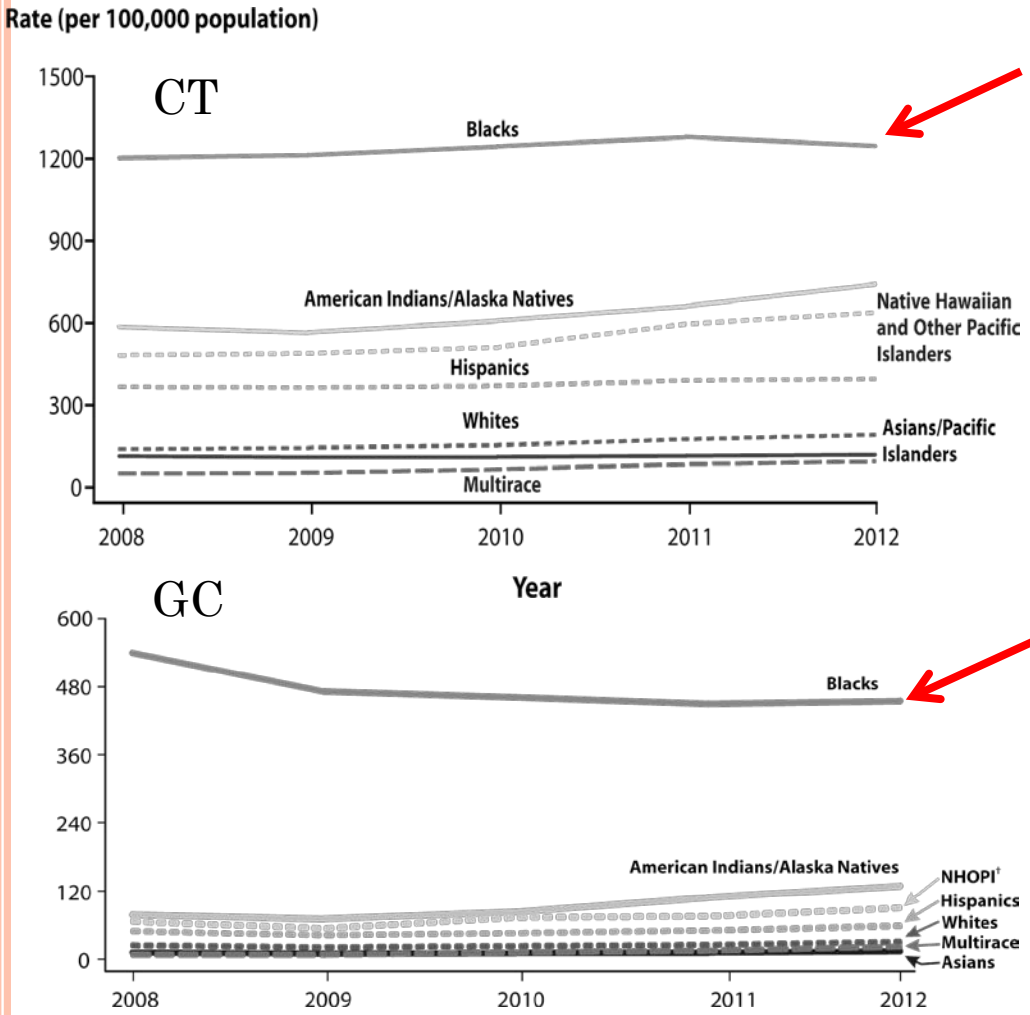


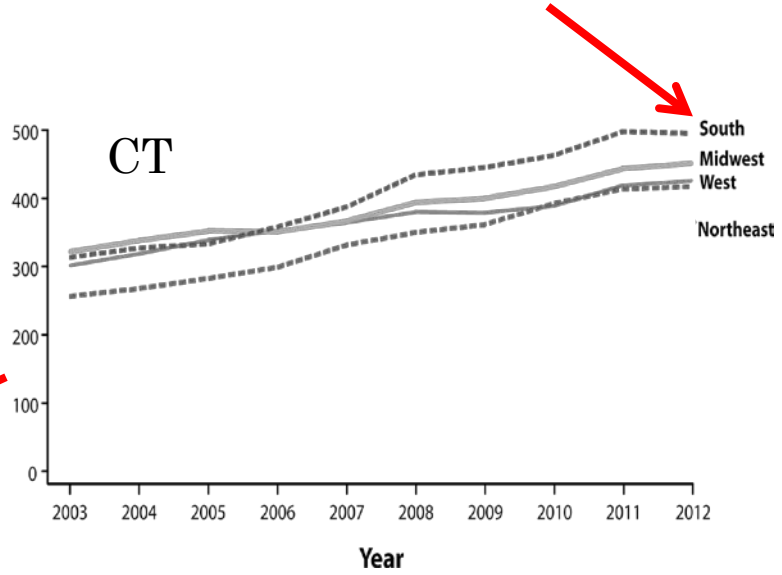
*Over 5 survey cycles, based on odds ratio from a logistic model using survey year as a continuous variable
†Numerator <10 positive sample persons
‡Relative Standard Error ≥ 30 but <40
§Relative Standard Error ≥40 but <50
¶Relative Standard Error=69, Numerator=2
‖p<0.05 for test of change in prevalence not equal to zero

SEXUALLY TRANSMITTED DISEASES

Datta et al, STD 2012

Regional as Well as Racial Disparities





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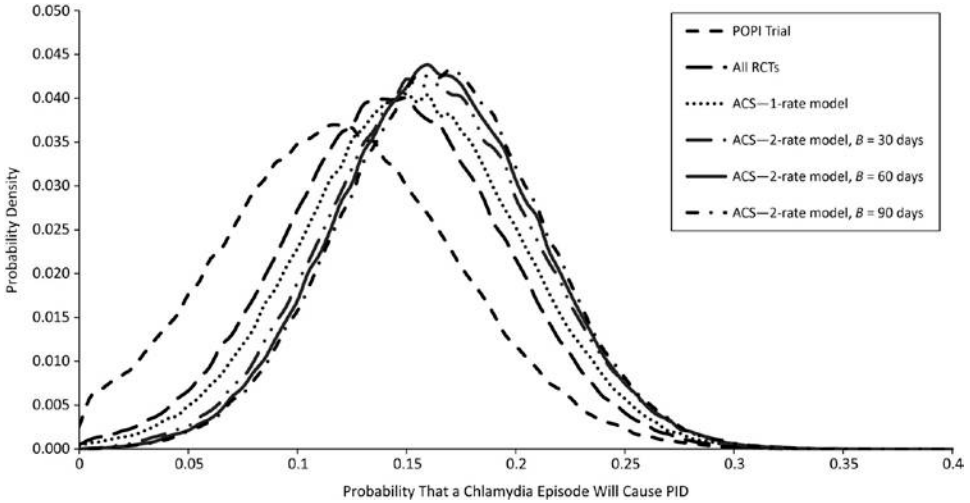
Negative Outcomes

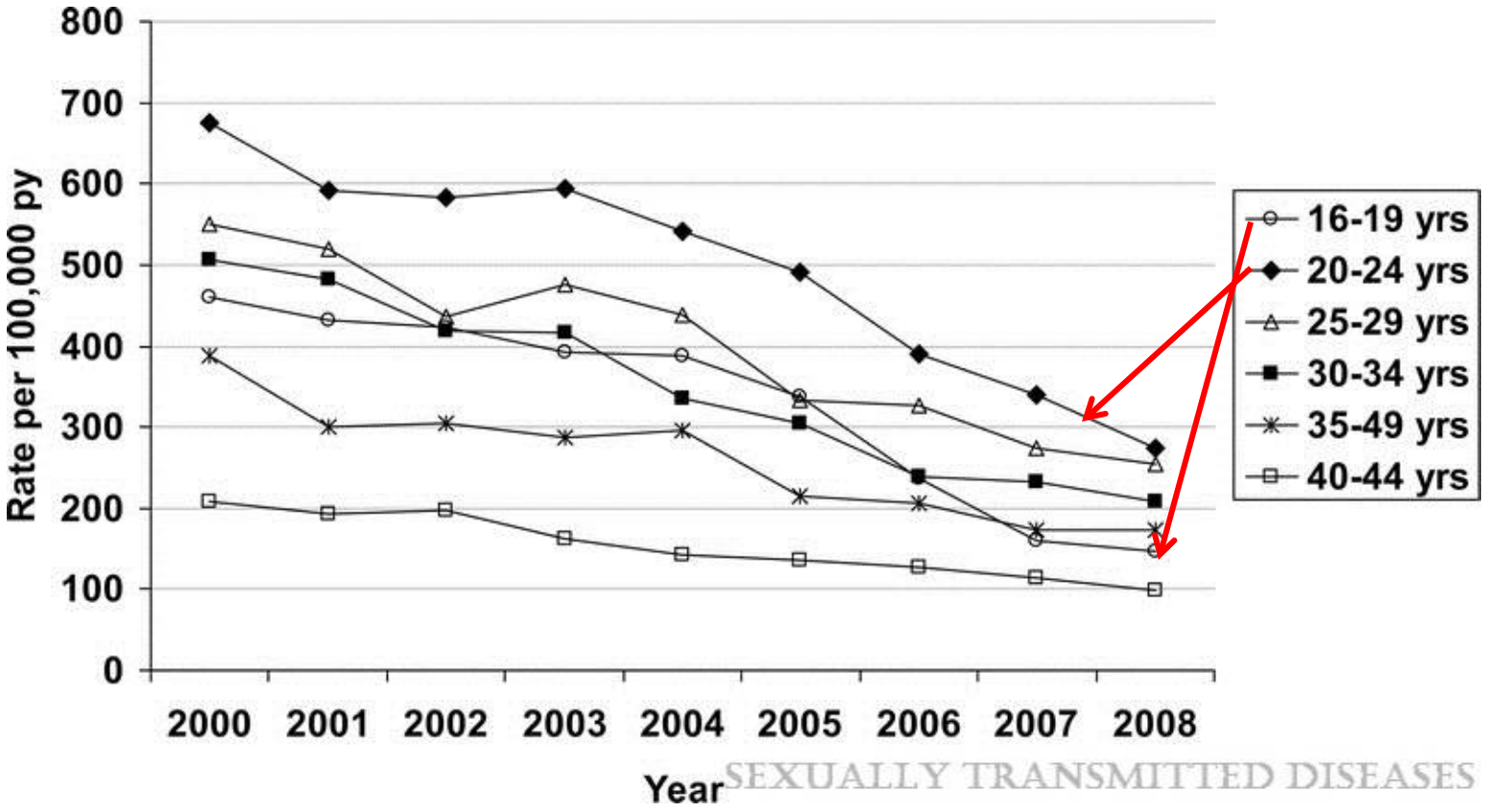
Negative Outcomes

- Reproductive Health
  - Pelvic Inflammatory Disease
  - Ectopic Pregnancy
  - Tubal Factor Infertility
- PID estimates ~16% chance of PID following infection
- Annual screening could reduce the rate by 61%



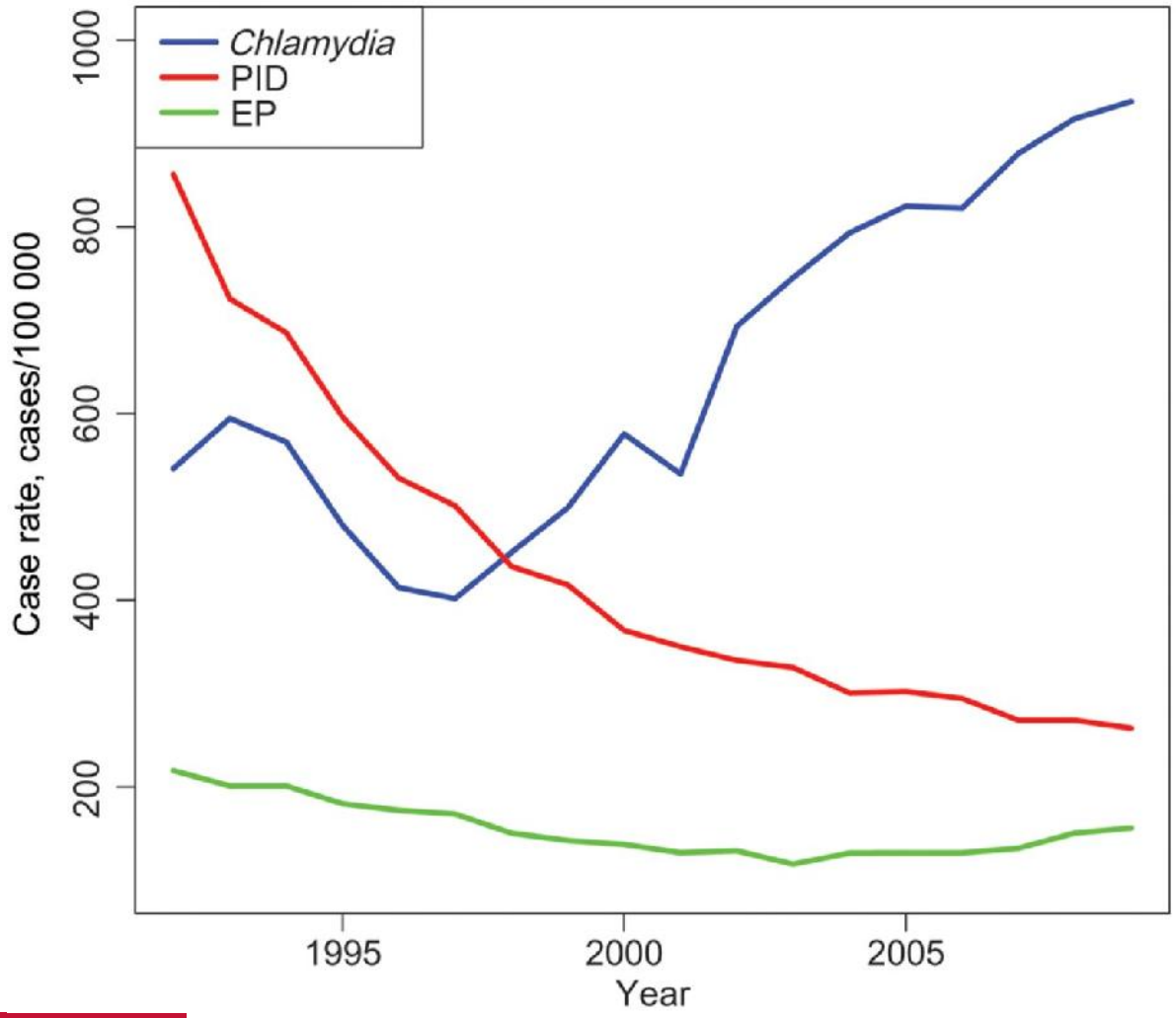
Price et al, AJE 2013

Rate of definite/probable PID diagnoses, England, 2000 to 2008



French et al, STD 2011

Case rates for *Chlamydia trachomatis* infection (age, 15–39 years), pelvic inflammatory disease (age, 15–44 years), and ectopic pregnancy (age, 15–44 years), British Columbia, Canada, 1992–2009.



The Journal of Infectious Diseases

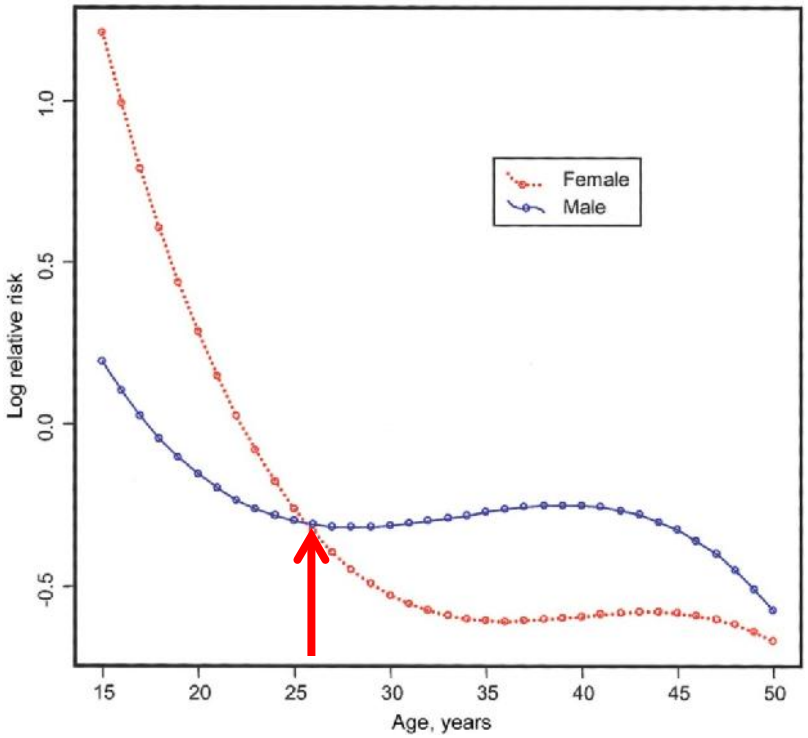
Rekart M L et al. J Infect Dis. 2013;207:30-38

Putting it all Together

- Case rates are rising (in women & men)
  - This is NOT explained solely by increased testing
  - Disparities persist
- PID rates are decreasing
  - Ectopic pregnancy and tubal factor infertility are more complicated to assess
- Control Programs are Warranted

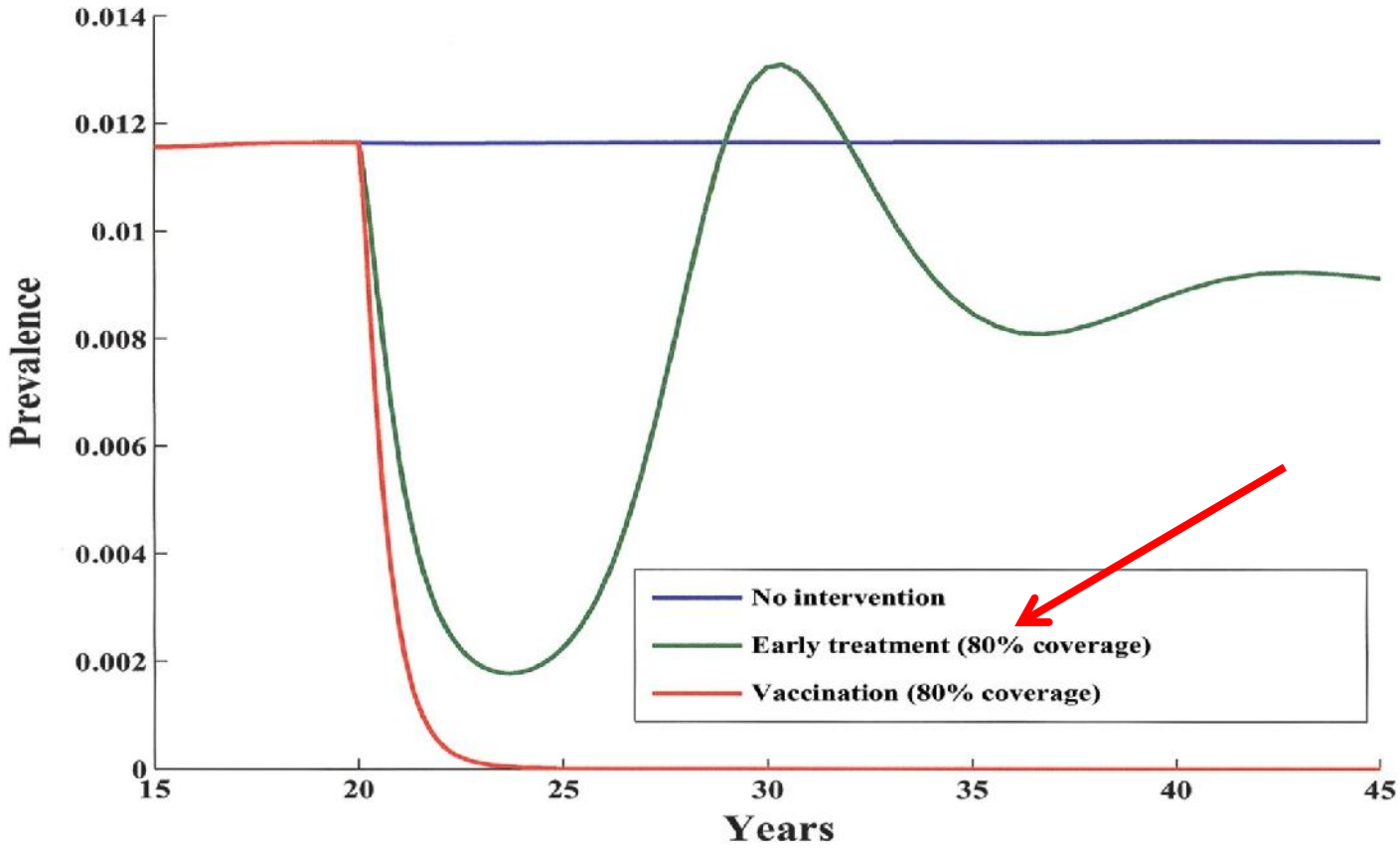
Treatment Guidelines: Cover WHO should be screened WHEN

- Urogenital Screening
  - All women ≤25 annually
  - Women or men who report "risky behavior"
  - Men who have sex with men
- Extra-genital Screening
  - Annually for all men who have sex with men



Brunham R C et al. J Infect Dis. 2005

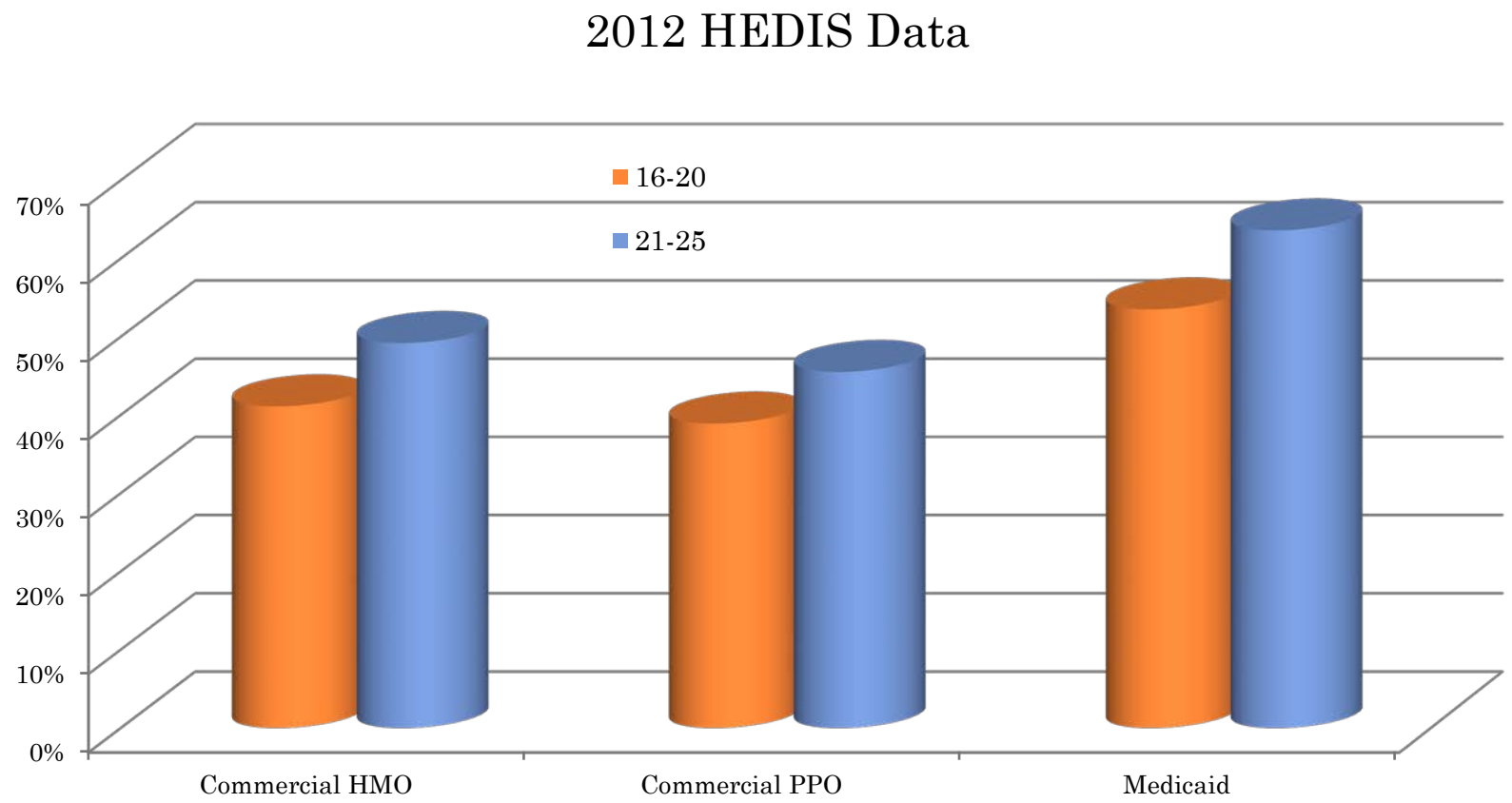
Impact of control strategies



The Journal of Infectious Diseases

Brunham R C et al. J Infect Dis. 2005;192:1836-1844

Are we nearing 80% Coverage?



May reflect discomfort discussing sexual health

Laboratory Diagnostic Guidelines

HOW GUIDELINES WERE DEVELOPED

- First update since 2002
  - Technology, and our understanding of it, has changed!
- Intensive literature review
  - Facilitated by NIH library scientists
  - Pulled all published articles and peer-reviewed abstracts meeting keyword criteria
  - Categories
    - Comparisons of assays
    - Evaluations of extra-genital specimens
    - Evaluations of self-obtained specimens
- Working group developed guidelines in Jan 2009
  - A rocky road to publication!

WHAT ARE THE RECOMMENDATIONS: *CLASS OF TEST*

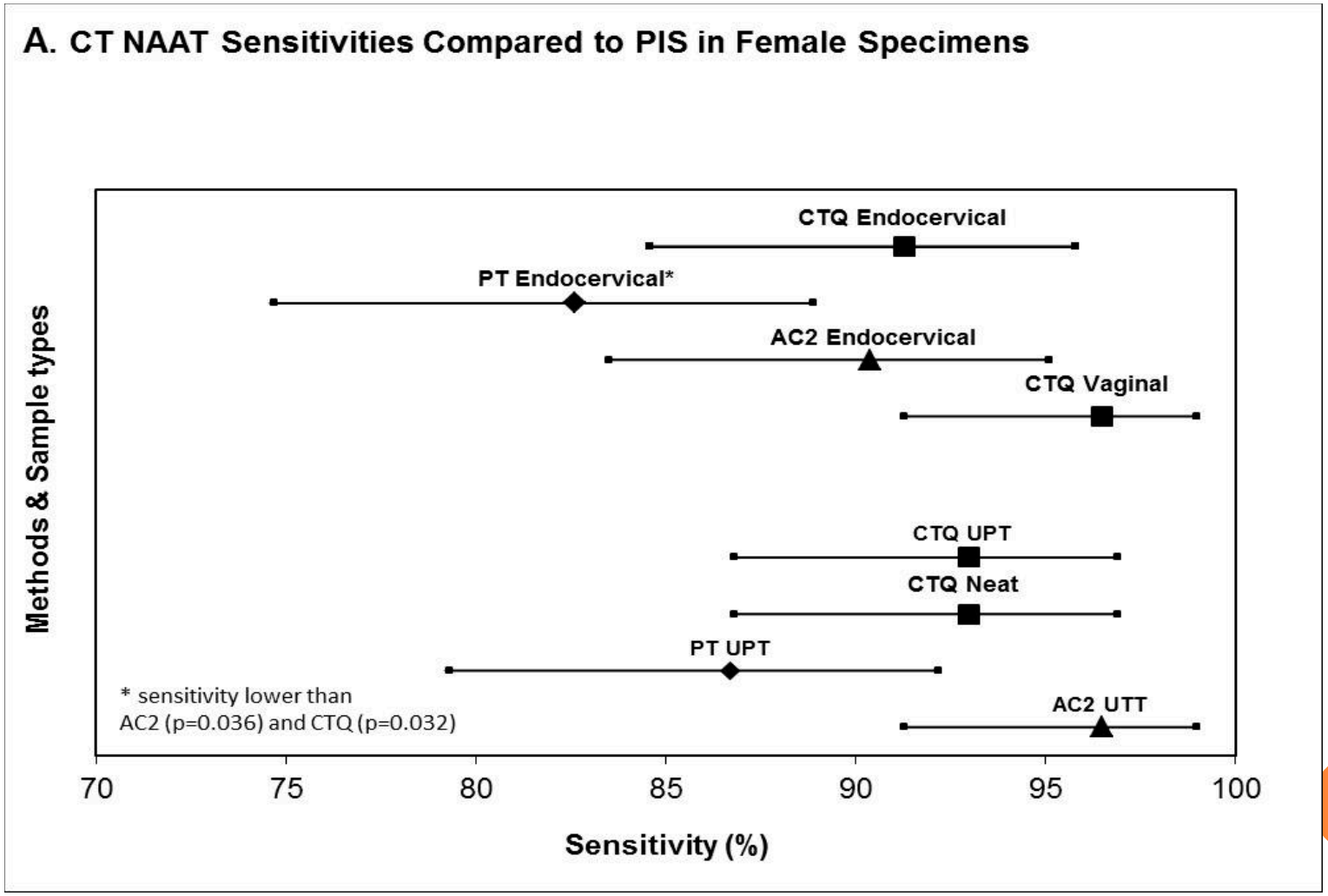
- Nucleic Acid Amplification Tests (NAATs)
  - Non-Amplification tests specifically discouraged
- No distinction for screening versus diagnostic testing
  - Individual work-up of symptomatic patients may required different strategies

Papp et al, 2014, MMWR

Impact of Tarnished Gold Standard

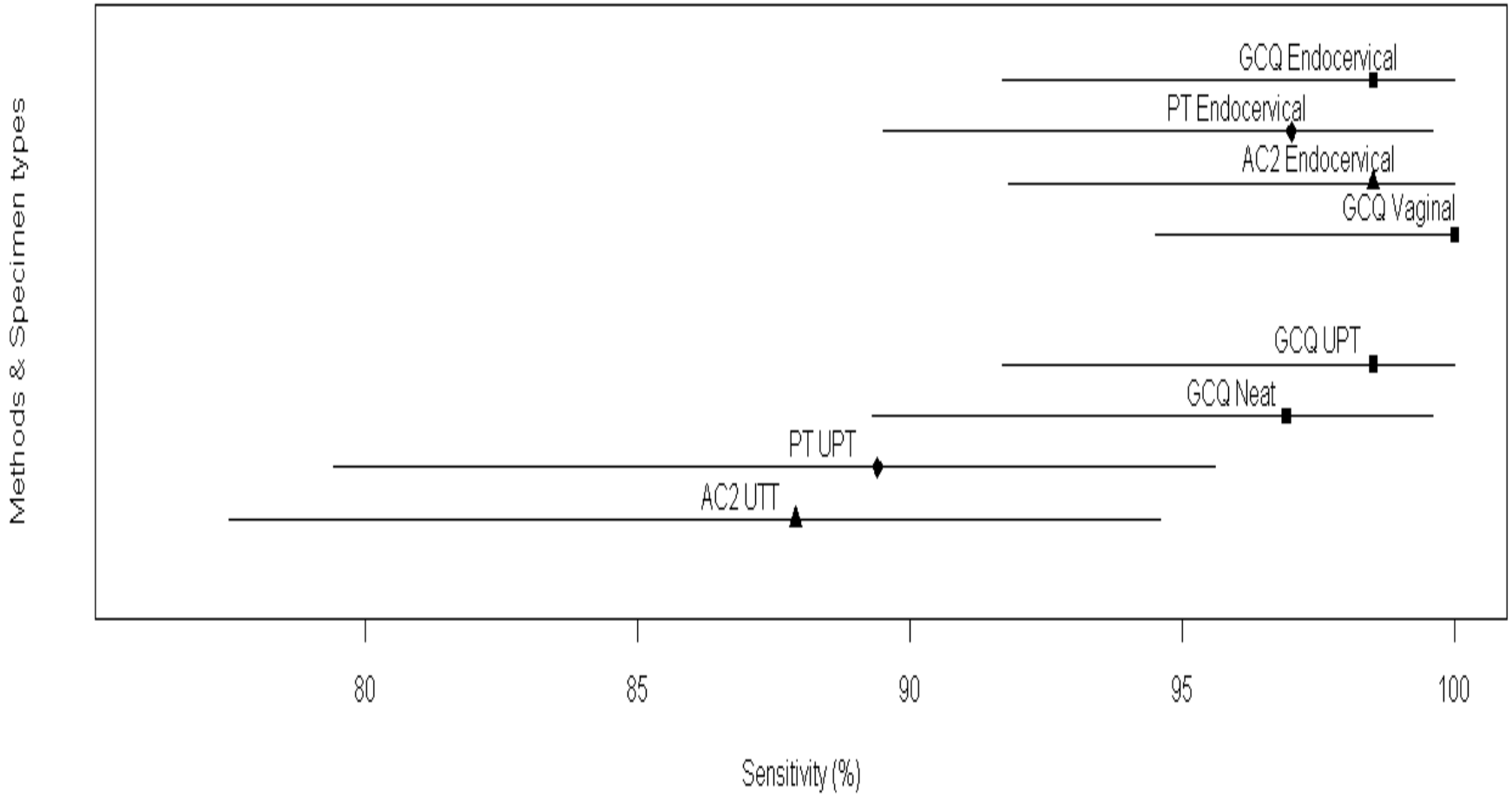
- 2002 Guidelines were based on early evaluations
  - Package insert data were meaningless by 2009!
- Sensitivity was overestimated for poor assays
- Specificity was underestimated for improved assays
  - Thus, 2002 guidelines recommended confirmatory testing
- Next-generation test have improved sensitivity & specificity
  - ***Confirmatory testing no longer recommended***

Examples of Next-Generation Assays



Taylor, et al STD 2011

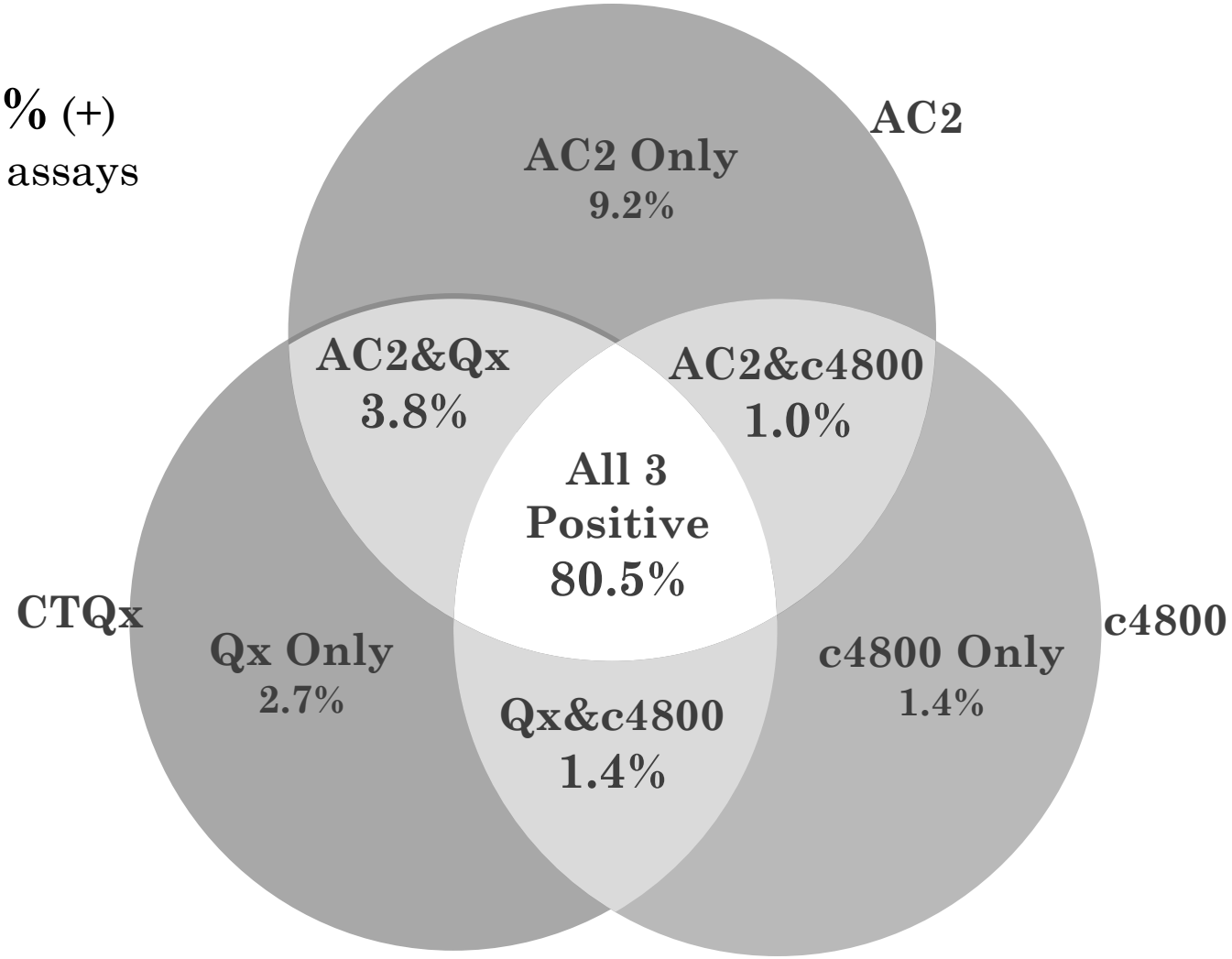
GC NAAT Sensitivities Compared to PIS in Female Specimens



Van Der Pol, et al STD 2012

CT Head-to-Head Comparison

86.7% (+)
by ≥2 assays



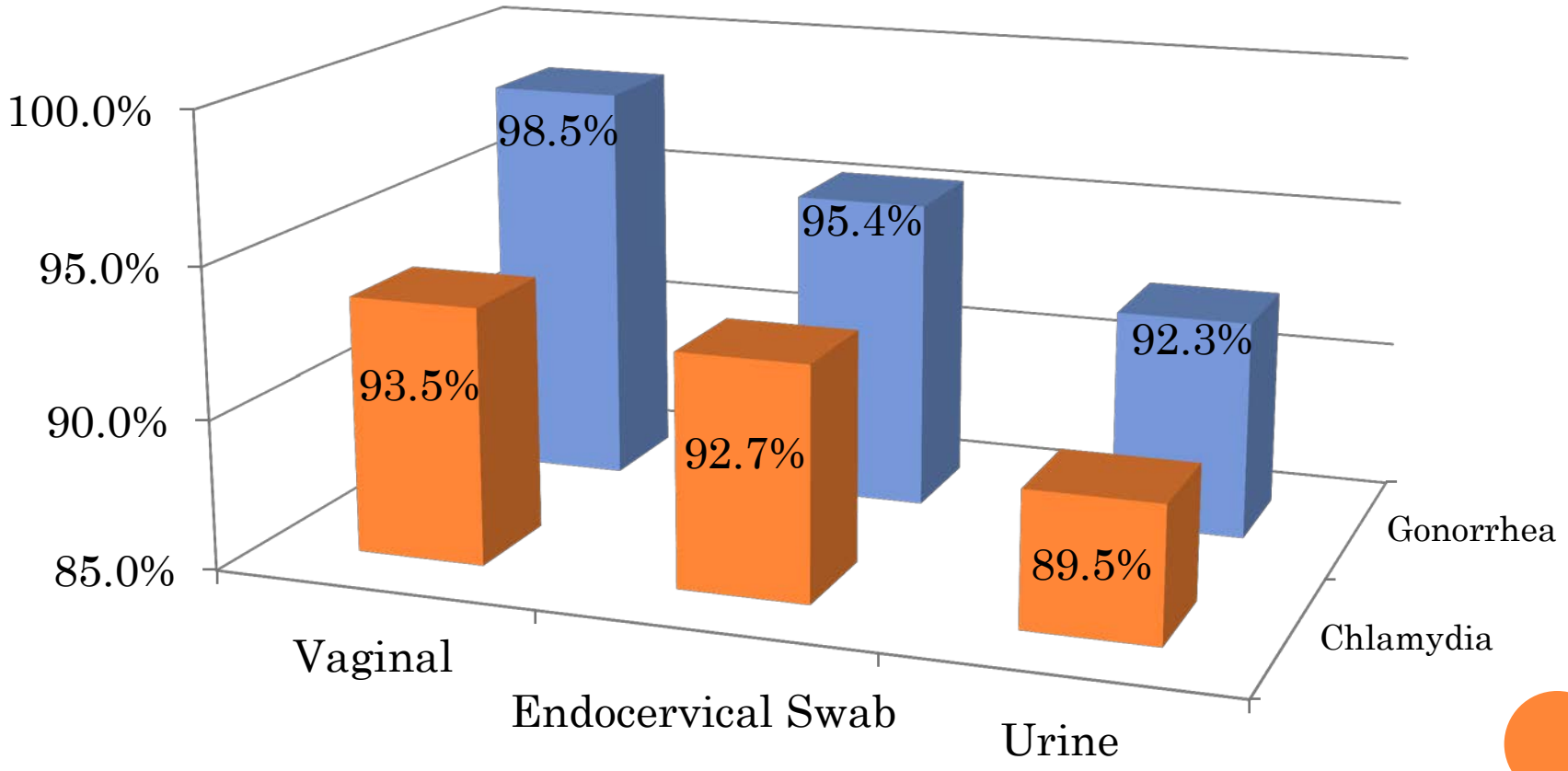
Van Der Pol, et al STD 2013

WHAT ARE THE RECOMMENDATIONS: *WOMEN*

- NAATs are the class of test that should be used
- **Self- or clinician-collected vaginal swabs** are the recommended sample type
- Endocervical swabs are acceptable when a pelvic exam is indicated
- First-catch urine is acceptable but may miss up to **10%** of infections
- Endocervical swab for GC culture is warranted if treatment failure is suspected

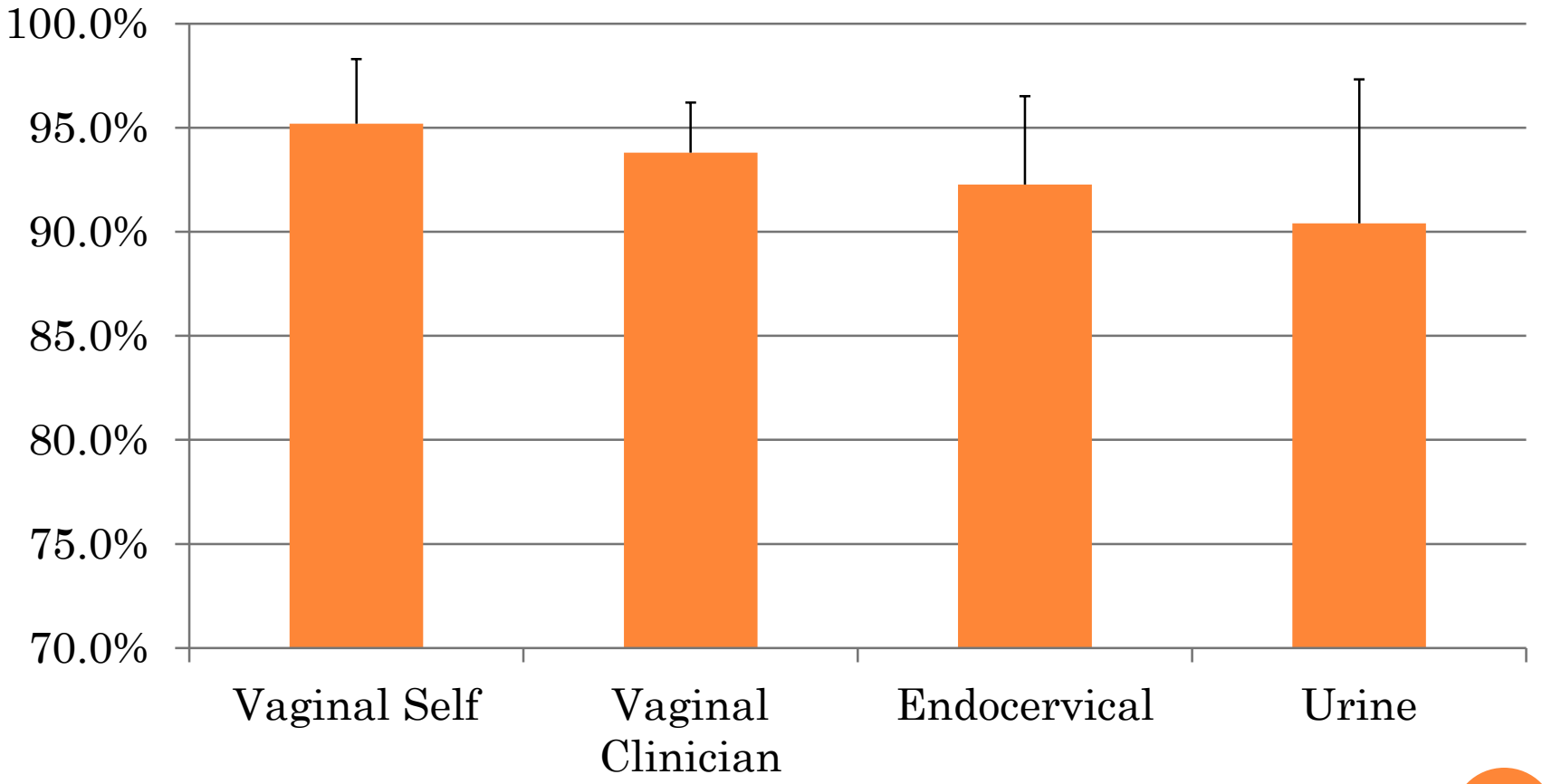
Papp et al, 2014, MMWR

Sample Type Comparison



Adapted from Van Der Pol, et al, 2013 STD

Chlamydia Sensitivity of Sample Types



Adapted from: Schachter et al. JCM 2003, Van Der Pol, et al. JCM 2012, Van Der Pol, et al. STD 2012, Gaydos et al. JCM 2013

Is the Difference Meaningful?

- Usually the order of sensitivity is:

  Vaginal> Endocervical>Urine>LBC

  - This is a consistent finding spanning >10 years and seen on EVERY major diagnostic platform
  - A meta-analysis of all clinical trial data would be useful

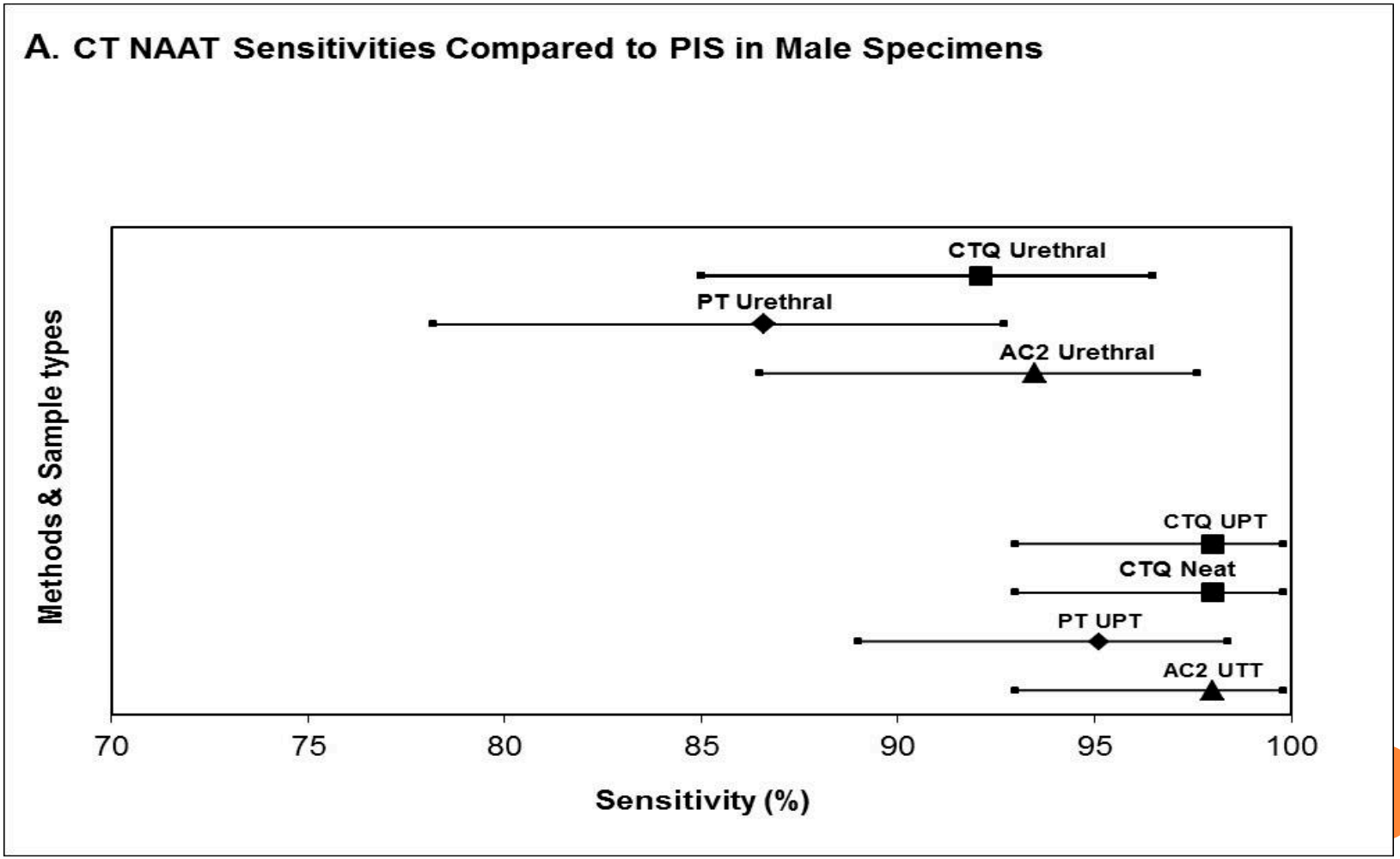
- Clinician and patient-obtained vaginal swabs are ***equivalent in quality***, but there may be other advantages to patient-obtained sampling

WHAT ARE THE RECOMMENDATIONS: *MEN*

- NAATs are the class of diagnostic that should be used
- First-catch-urine is the recommended sample type
  - Data review did not provide evidence of improved sensitivity of urethral swabs
- Urethral swab for GC culture is warranted if treatment failure is suspected

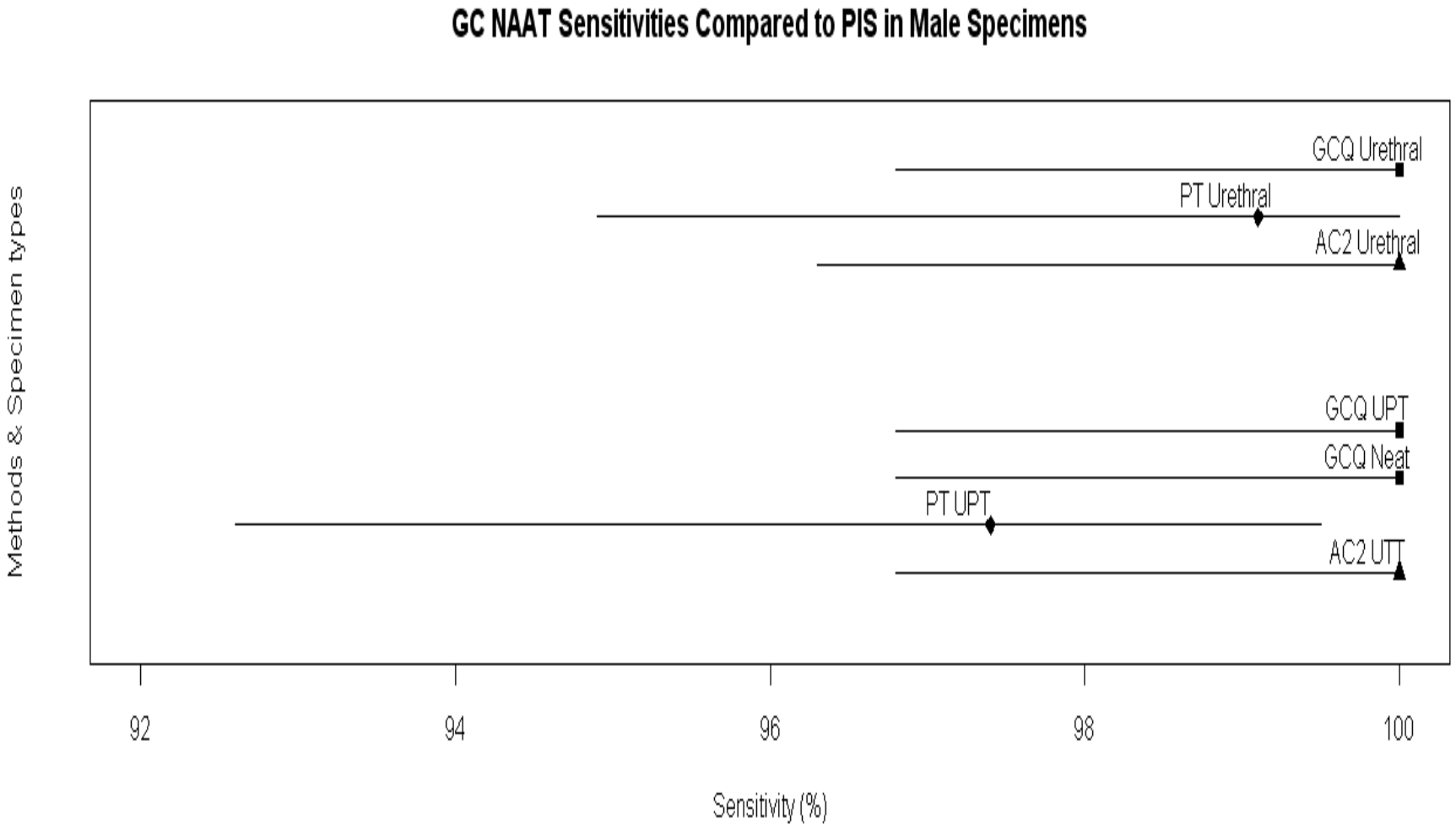
Papp et al, 2014, MMWR

CT Sensitivities for Men



Taylor, et al STD 2011

GC Sensitivities for Men



Van Der Pol, et al STD 2012

WHAT ARE THE RECOMMENDATIONS: *EXTRA-GENITAL TESTING*

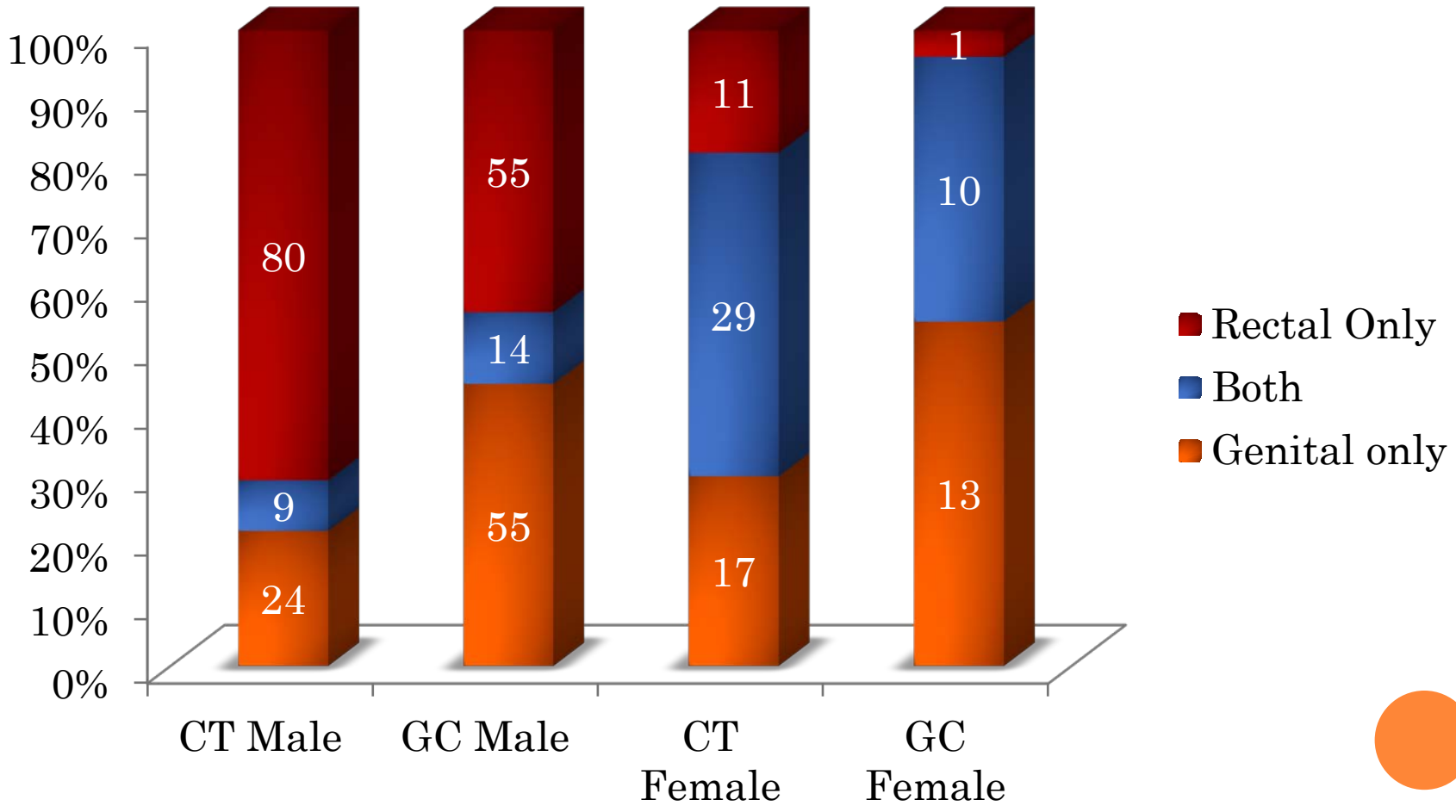
- NAATs should be used for Rectal & Oropharyngeal samples
- Treatment guidelines recommend annual screening men who have sex with men
  - Studies suggest screening everyone regardless of reported behavior may be beneficial
- ***No*** *assay has FDA clearance for these sample types*
  - *Our lab has validated several assays and will continue validating newer assays*

Papp et al, 2014, MMWR

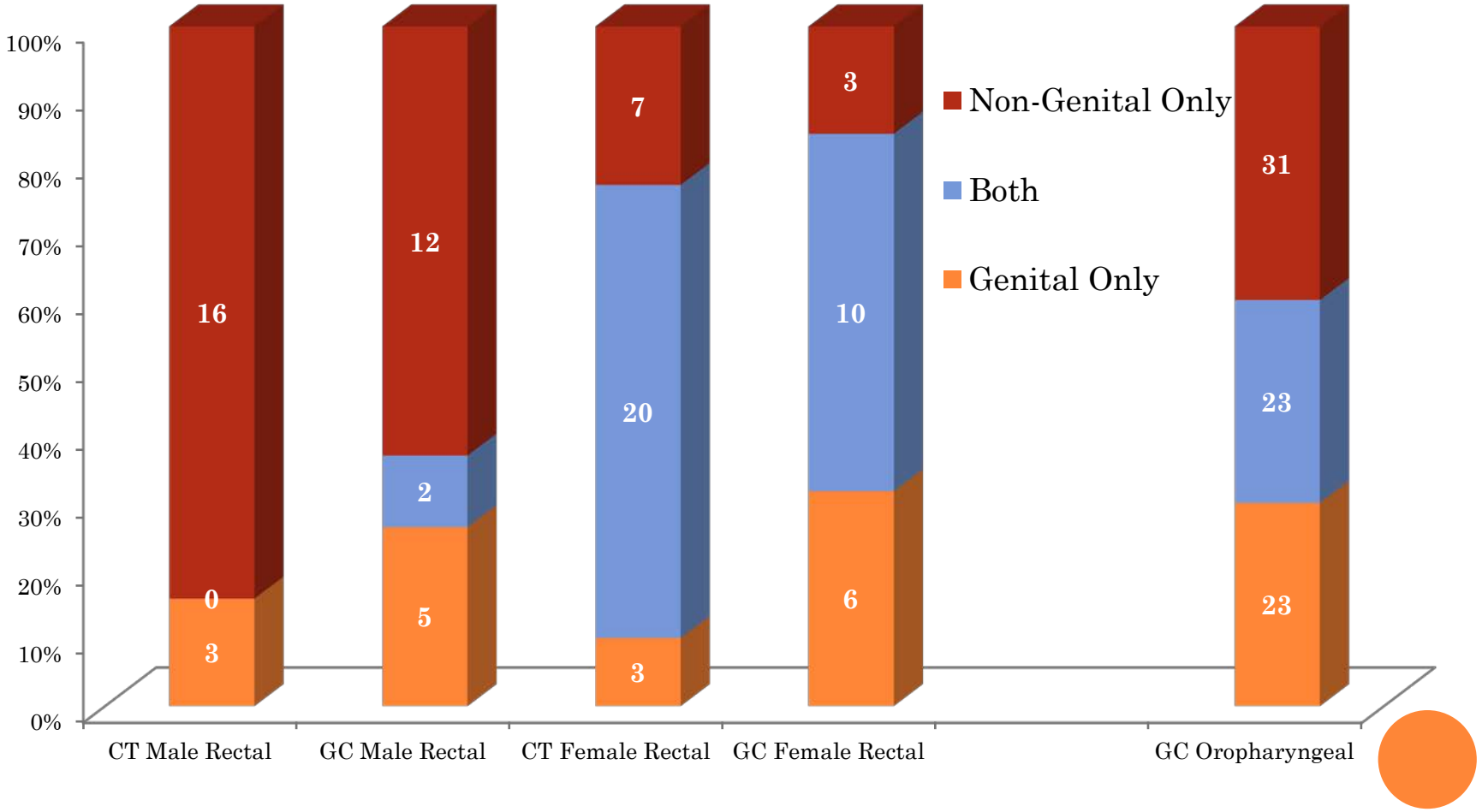
Indianapolis STD Clinic Data, 2011

10,868 clients	Men	Women
CT Genital	19.1%	13.9%
CT Throat	1.1%	1.9%
CT Rectal	**17.2%**	**10.8%**
GC Genital	6.6%	4.4%
GC Throat	2.3%	3.0%
GC Rectal	2.3%	2.2%

Proportion of Infections Detected by Rectal or Genital Sampling



Birmingham Data



Adapted from Bachmann, et al, JCM 2009

If it is Difficult to get clearance for Genital samples…

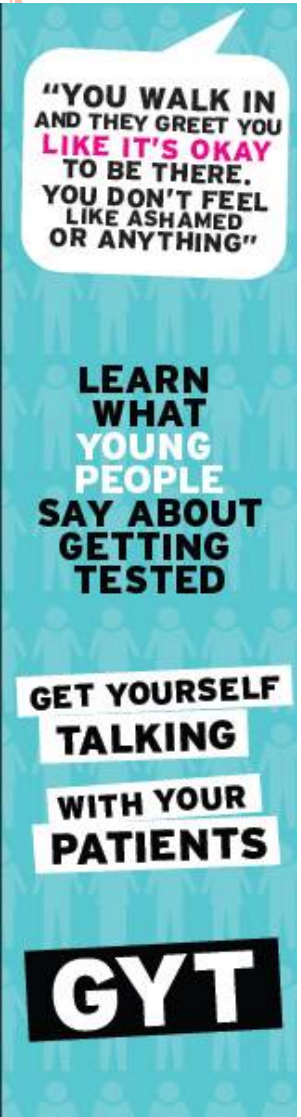
- Despite the recommendation for male urine, FDA still requires at least 1 urethral swab for comparison
- Will we ever have a diagnostic with claims for rectal specimens
  - Do YOU want to provide 3-4 samples for comparisons?
- Validation requires
  - Paired samples
  - Access to previously tested samples
  - Organisms to spike into samples

Summary of Recommendations

- NAATs
  - No confirmation required
- Vaginal swabs or male urine
- NAATs for rectal & oropharyngeal samples
  - ***Must be validated locally***
- Culture capacity needs to be maintained
  - GC susceptibility testing
  - CT & GC for some cases for child sexual abuse testing

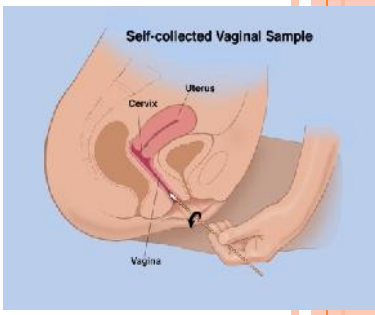
Using the Guidelines to Improve Services

How do the recommendations improve clinical service?

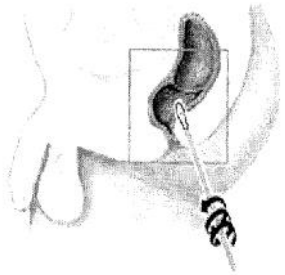


- Better performing assays increase case-finding AND reduce false-positive results

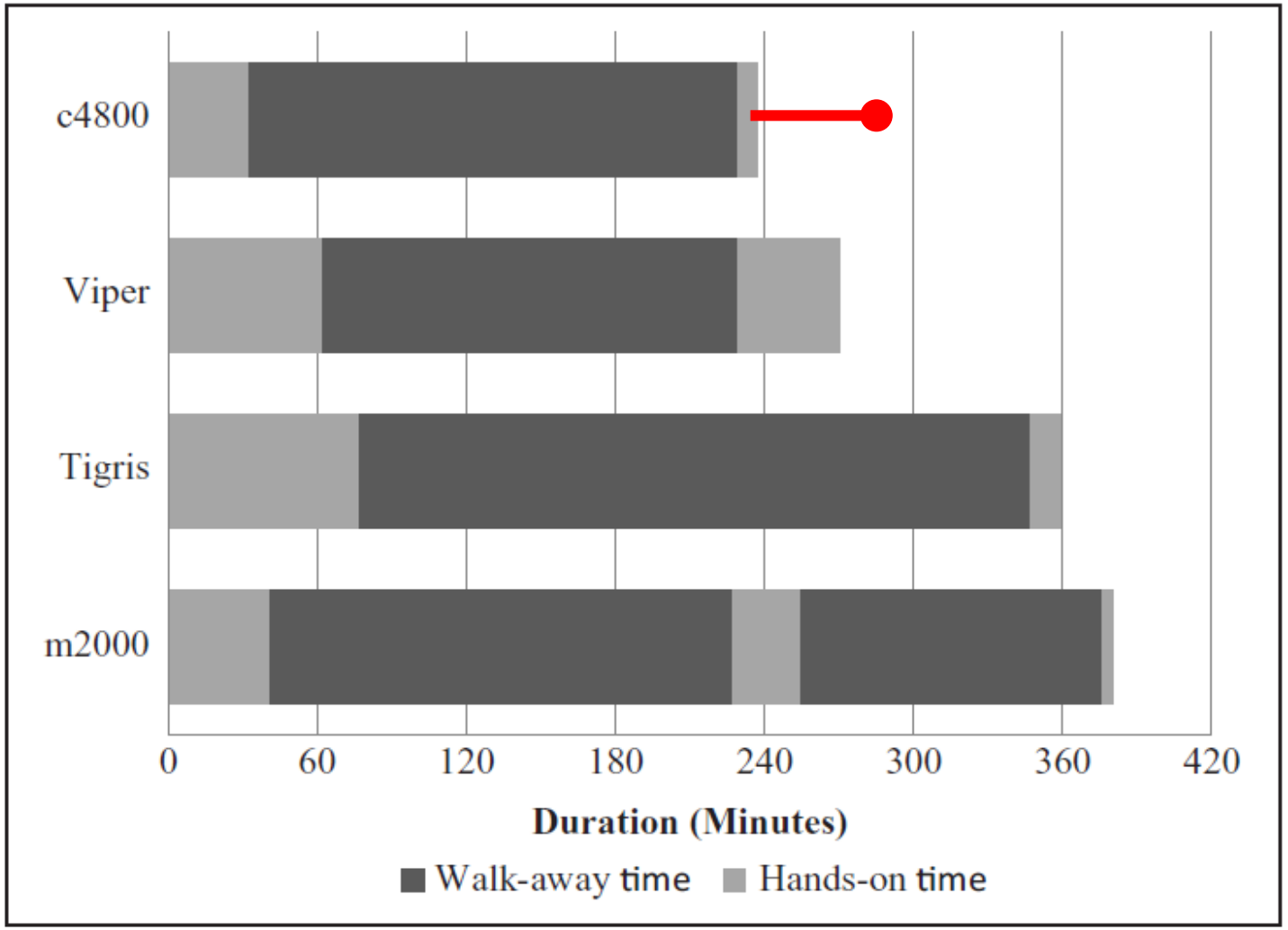
- Patients can self-collect samples before seeing a clinician
  - "***Routine" urine is a poor sample***
  - Frees clinician time, may improve clinic flow,
  - Involves patients in their own healthcare, may "normalize" screening



- Extra-genital sampling may improve case-finding
  - Particularly relevant for men who have sex with men

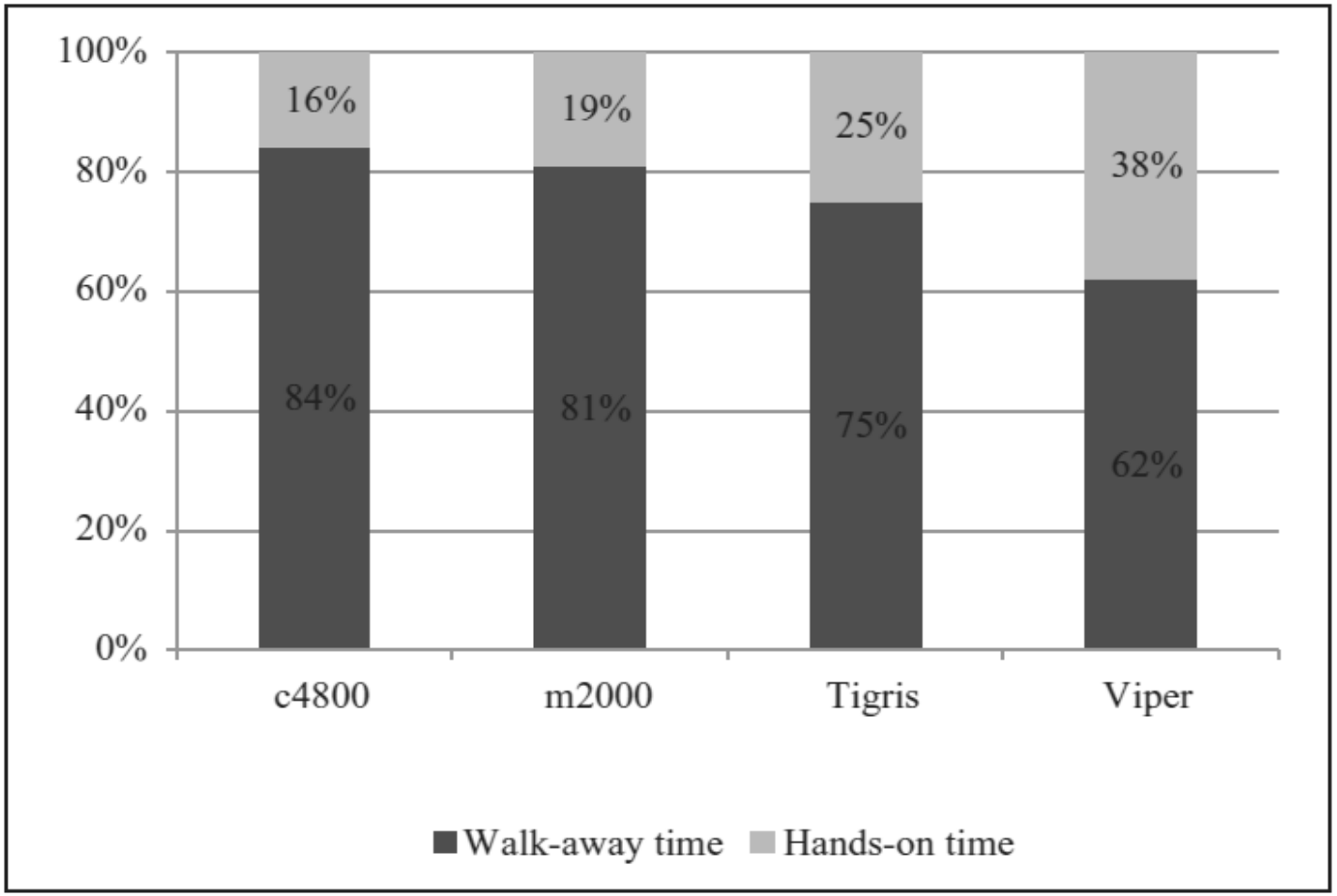


The Lab Benefits Too



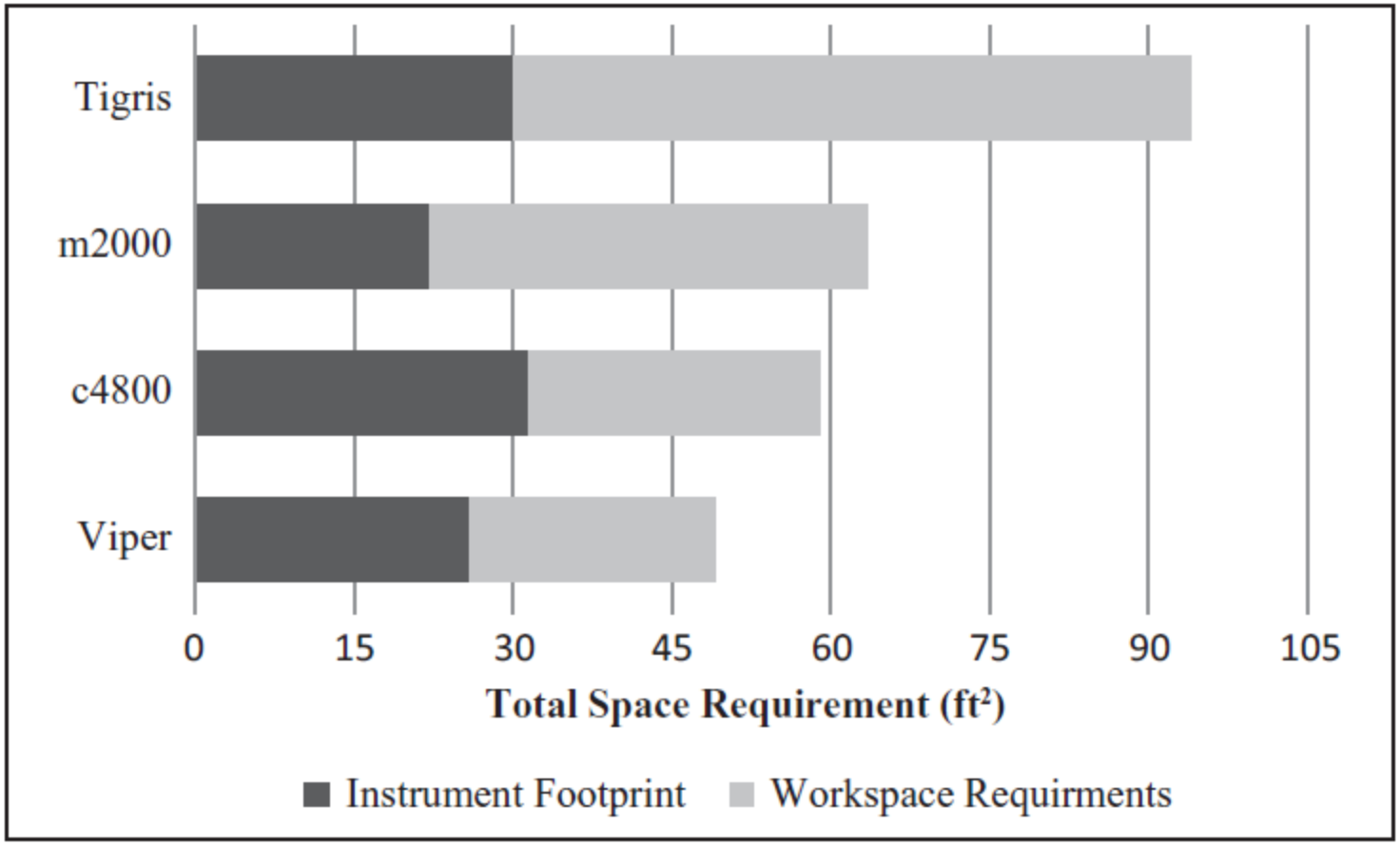
Williams, et al STD 2013

Percent Walk-Away Time



Williams, et al STD 2013

Space…



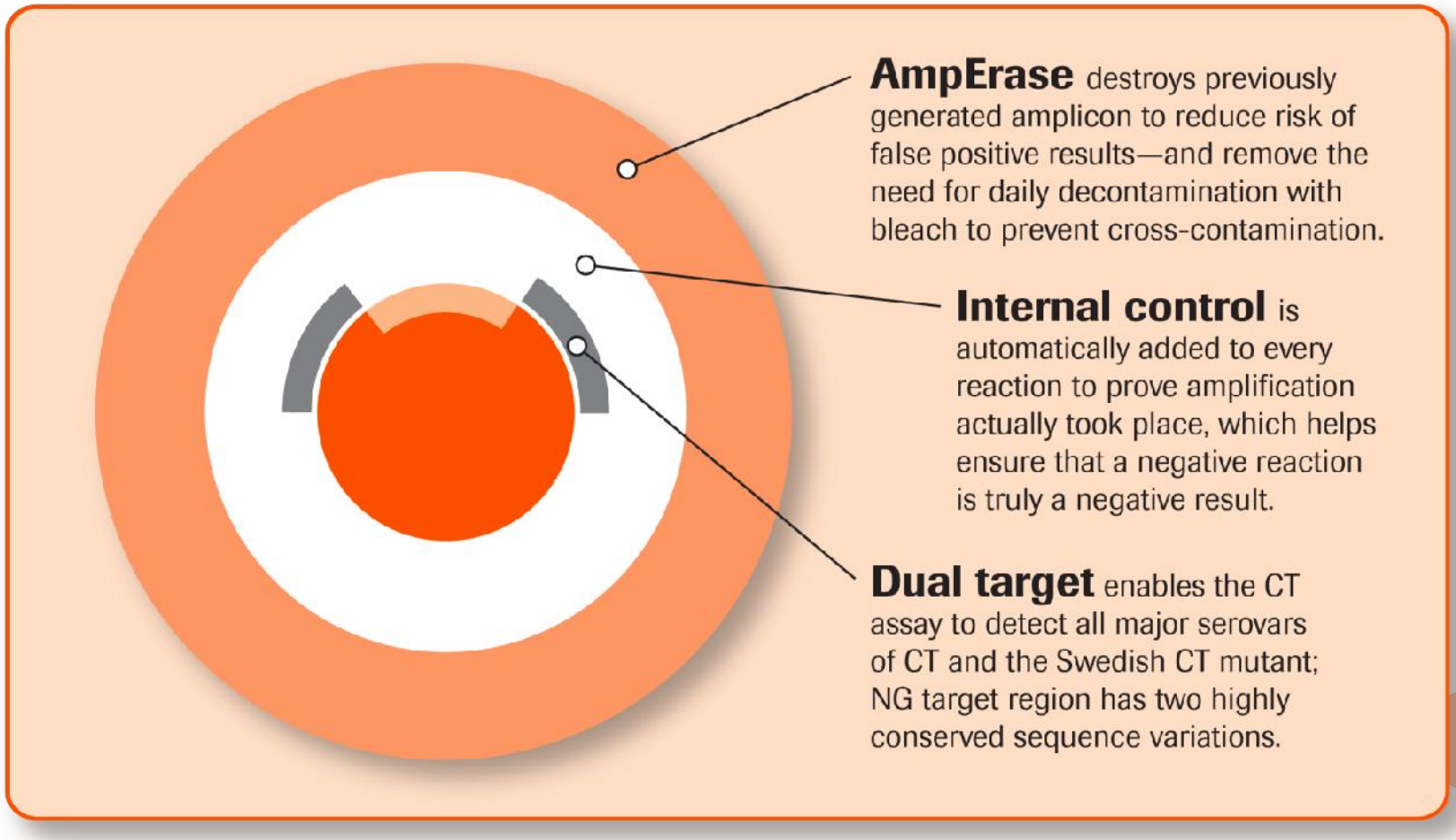
Williams, et al STD 2013

COBAS CT/NG TEST IS THE ONLY NEXT-GENERATION TEST WITH DUAL-TARGETS

Chlamydia trachomatis	Neisseria gonorrhoeae	Internal Control
• Detects both cryptic plasmid and ompA gene Major Outer Membrane Protein (MOMP) targets • Detects all major serovars of CT and the Swedish CT mutant (nvCT) • Detects variants that may harbor deletions in the cryptic plasmid • Detects variants that do not carry the cryptic plasmid	• Detects both the Direct Repeat (DR9) sequence A and the Direct Repeat (DR9) sequence B targets • Target region is repeated x3 in the NG genome and has 2 highly conserved sequence variations • Detects combinations of both target variations • No cross-reactivity with commensal Neisseria or other bacterial species has been observed	• Two individual IC plasmids provide consistent signal with high target input

Dual-probe, single-tube multiplex assay design with automatic internal control

Laboratory Confidence = Clinician Confidence



Final Thoughts

- Options that improve adherence to Screening Guidelines are needed
  - We need to consider ways to involve men in screening efforts
- Use of next-generation NAATs may extend our reach/coverage
  - Self-obtained samples can be used in non-traditional settings and may improve clinic flow
  - Extra-genital testing may improve case-finding in some populations
  - High confidence in quality of results may encourage providers to test more patients

Thanks for Your Attention

Alabama – North Carolina
STD HIV
Prevention Training Center