Appendix 3: Screening for Chlamydia and Gonorrhea: Evidence to Decision Framework

Should non-pregnant sexually active individuals be screened for Chlamydia and/or Gonorrhea?

POPULATION:	Non-pregnant sexually active* individuals of any age
INTERVENTION:	**KQ 1&2:** Any approach to screening for chlamydia and/or gonorrhea **KQ3:** Experience with a screening program for chlamydia and/or gonorrhea; experience with infection or outcomes of interest; exposure to scenarios about screening process and possible outcomes of screening (benefits and harms)
COMPARISON:	**KQ1:** No screening **KQ2:** Any screening comparison differing from the intervention by the following factors: a) Opportunistic vs. risk-based testing; b) Health care setting only: sample collection location (i.e., clinic/health care setting vs. home); c) Outreach screening only: offered through street-based (e.g. mobile van) vs. other venues (e.g. bars, community services, bath houses, sporting events); d) Sample collection method (i.e., urine vs. culture; genital vs. genital and extra-genital); e) Sample collection personnel (i.e., self vs. health care provider); f) Screening interval (i.e., one-time vs. annual vs. less frequent); g) Case management approaches **KQ3:** Could include no screening or another form of screening, or study may have no comparator.
MAIN OUTCOMES:	**Critical:** • pelvic inflammatory disease (PID; females); • ectopic pregnancy (females); • infertility (females and males); • chlamydia/gonorrhea infection transmission (females and males); • cervicitis (females); • chronic pelvic pain (≥6 months duration/females); • repeat infection/reinfection (KQ2 only); **Important:** • negative psychosocial impact from screening procedure or the results of a positive diagnosis; • serious adverse drug reaction from antibiotic treatment.
SETTING:	Primary care settings in Canada
PERSPECTIVE:	Population

BACKGROUND:

Chlamydia (CT) and gonorrhea (NG) are the most commonly reported bacterial sexually transmitted infections (STIs) in Canada, with rates of both having increased significantly over the past decade, and co-infection being common. Rates vary depending on sex (CT higher among females), age (more common among those aged 15-29), geography (more common in Nunavut and the northern territories), membership in a vulnerable group (e.g., higher rates among sex trade workers), and sexual behaviours.

While both chlamydia and gonorrhea are treatable once identified, most cases are asymptomatic and therefore many go untreated. In females, CT and NG infection can lead to important outcomes such as inflammation of the urogenital tract, pelvic inflammatory disease, chronic pelvic pain, ectopic pregnancy, and infertility. For males, untreated infection can lead to inflammation of the urogenital tract and potentially infertility in rare cases. Untreated CT and NG are also likely to be transmitted among sexual partners.

Screening for CT and NG involves offering tests to patients whether they have symptoms or not so that treatment and follow-up can be provided. In Canada, screening is most commonly offered opportunistically by clinicians in a variety of primary care settings (e.g., family practice, sexual health clinics, school health centres) during visits that may or may not be for sexual health-related concerns. This is distinct from a systematic population screening program.

The screening tests for CT and NG involve taking a swab from one or more locations (genital, oral) or providing a urine sample, which can be analyzed in a laboratory using nucleic acid amplification tests (NAAT; gold standard) or culture to determine if CT or NG are present.

CT and NG infections are treated with antibiotics. They are reportable infections in Canada, involving regional public health authorities and contact tracing.

Appendix 3 (as supplied by the authors). Appendix to: Moore A, Traversy G, Reynolds DL, et al; for the Canadian Task Force on Preventive Health Care. Recommendation on screening for chlamydia and gonorrhea in primary care for individuals not known to be at high risk. *CMAJ* 2021. doi: 10.1503/cmaj.201967.

*Studies for KQ3 that reported on health state values for people with experience of the outcomes of interest that may have been caused by another infectious source do not have to only include sexually active individuals.

Assessment

	JUDGMENT	RESEARCH EVIDENCE
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes X **Yes** ○ Varies ○ Don't know	**Problem** **Judgment** Screening for chlamydia (CT) and gonorrhea (NG) is judged by the Task Force to be a priority problem. This is based on burden of disease in Canada (the number of people affected) increasing rates of infection, the potential consequences of untreated infection, the treatable nature of the condition, and important uncertainty for practice. **Number of people affected (burden)** • Canadian rates are increasing for CT: by 49% (206 to 307 per 100,000) and for NG: by 61% (28 to 46 per 100,000) from 2005-2014 (1). • 2017 rates: reported cases highest in 15-29 year olds (1.0-1.9% for CT and 0.2-0.3% for NG). Rates among individuals over 30 years old were <0.5% for CT and <0.2% for NG (2). • Likely higher burden than what is reported, as many infected individuals are asymptomatic, do not seek care and are not included in reported rates. Taking underreporting into account, true CT prevalence in 15-29 year-olds may be as high as 5-7% (1-4). **Potential Consequences of untreated CT and NG** • **Females:** cervicitis (affecting an estimated 10-20% of females with untreated chlamydia infections) (5), pelvic inflammatory disease (PID) (10-16% of CT, may be higher for NG) (6,7), infertility (up to 5% of CT cases) (8), chronic pelvic pain (3-8% of CT) (8,9) and ectopic pregnancy (up to 2% of CT) (8) • **Males:** epididymitis (up to 7% of CT) with or without orchitis (4,10) and very rarely infertility (11) • **Both sexes:** urethritis (up to 3% of males and 4% of females who are infected with CT) (12), pharyngitis, proctitis, reactive arthritis (lasting over 6 months in 1-4% of cases of CT or NG) (13,14) and very rarely disseminated gonococcal infection (<1% of NG), which can in some cases lead to sepsis, meningitis, endocarditis and osteomyelitis (15) **Uncertainty for practice** • National guidance from the Public Health Agency of Canada (2010) was not based on a systematic review of the evidence and does not include screening recommendations for NG (16,17).

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects (general risk)?

○ Little to no difference
X Small
○ Moderate
○ Large

○ Varies
○ Don't know

Anticipated desirable effects (Benefits)

GENERAL RISK POPULATIONS - CHLAMYDIA SCREENING

All studies (9 randomized controlled trials (RCTs) (3,4,6,18-23), 1 controlled clinical trial (CCT) (24), and 2 retrospective cohort studies (25,26)) on potential screening benefits provided indirect evidence (i.e., low applicability) on how and to whom screening would be offered in Canadian primary care. For example, 4 RCTs offered screening (regardless of uptake) by mailed invitation or public education and screening encouragement (4,20) rather than via in-person discussion, and 1 cluster RCT provided clinic-level interventions (packages) (3) rather than direct clinician engagement, yielding low participation and offers of screening. Three trials evaluated only those accepting of screening (acceptors of screening) (6,19,24), and 1 trial evaluated an offer to screen among those pre-selected for an interest in screening (offer to screen, pre-selected) (22), which is indirect to the varied screening interest and acceptance among Canadian primary care patients.

Offer to screen, regardless of uptake

Meta-analysis of 2 RCTs (n= 141,362) found very low-certainty evidence for little to no difference in PID rate among females aged 16-29 over 1 to 3 years from an annual offer of CT screening (0.3 more in 1000 [95% confidence interval [CI] 7.6 fewer to 11 more]) (3,4).

One RCT (n = 15,459) found very uncertain effects on infertility and very low-certainty evidence for little to no difference in ectopic pregnancy rates for females aged 21 to 24 over 9 years from a single offer of CT screening (0.2 more in 1000 [95% CI 2.2 fewer to 3.9 more]) (4).

Meta-analysis of 3 RCTs (n = 41,709) found low-certainty evidence for little to no difference in CT transmission for those aged 15-29 years over 1 to 3 years from an offer of CT screening (5.4 fewer per 1000 [95% CI 21.0 fewer to 12.6 more) (3,18,20).

Offer to screen, selected individuals

One RCT (n= 2,607) among pre-selected females aged 18-34 (81% under age 24) found low-certainty evidence that offering a single screening may reduce PID (15.4 fewer per 1,000 [95% CI 3.0 to 21.3 fewer], NNS= 65 [95% CI 47 to 333]) (22).

Acceptors of screening

Two RCTs and one CCT (n= 30,652) found low-certainty evidence that females aged 15-29 who complete a single CT screen over 12-18 months may have a reduced risk for PID over 1 year (5.7 fewer per 1000 [95% CI 10.8 fewer to 1.1 more] (6,19,24).

Cervicitis, Chronic pelvic pain, Male infertility: No data available for chlamydia screening.

GENERAL RISK POPULATIONS - GONORRHEA SCREENING

No studies on the effects of screening NG for any outcomes of interest were identified in general risk populations.

Judgment – Screening for CT and NG

PID may be reduced for those accepting and undergoing screening (6,19,24) and for those interested in being screened (low certainty) (22). Very uncertain evidence found little to no difference in PID when CT screening was offered via mailed invitation or clinic-level packages encouraging screening (regardless of uptake). The task force judged that the true benefit of CT screening when offered in person by Canadian primary care practitioners, who are positioned to identify those eligible and offer screening opportunistically, would likely lie within this observed range of screening effectiveness.

Benefits of screening this population for NG are unknown due to lack of evidence for critical outcomes. However, current Canadian clinical and laboratory practice is to combine testing for NG with CT using a single sample, and most commercial NAAT assays test for both organisms simultaneously with a single specimen (27). Also, as with CT, many NG cases are asymptomatic (17,28) and identified only through screening. Additionally, up to 40% of those with NG may have CT (29-31).

In the judgment of the task force, the benefits of opportunistic screening for CT and NG via clinicians' offices are anticipated to be small but important, recognizing the very low certainty of the evidence.

Judgment - Comparing screening strategies

In the judgment of the Task Force, there was insufficient direct evidence to inform comparative effectiveness on home-based versus clinic-based screening and no available evidence to evaluate other comparisons of screening approaches including risk-based versus opportunistic approaches, or differing screening intervals for CT and NG screening (32).

GRADE Summary of Findings

Screening vs. no screening; Pelvic Inflammatory Disease (Offer to screen)

Included studies: Trials: Hocking 2018, Andersen 2011, Scholes 1996
Threshold for important effect: 2.5 per 1000 fewer [benefit] or more [harm]

Outcome No. participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of the evidence (GRADE)	What happens?
		Without screening*†	With a single CT screen	Difference		
Offer to screen – All eligible (based on age and sexual activity), regardless of uptake						
All-cause PID (Eligible participants) Follow-up: 12-36 mos	1.01 (0.72 to 1.40)	Median control event rate (5 per 1000)			⨁⨁◯◯— ⨁⨁⨁◯	Offering a single CT screen via opportunistic or population based approaches to all females 16-29 years old in
		5 per 1000	5.1 per 1000 (2.9 to 6.5)	0.1 more in 1000 (2.1 fewer to 1.5 more)		

141,362 16-29 yrs (2 RCTs)		General-risk population†			LOW-TO-MODERATE (Median control event rate with low PID prevalence)[a] due to indirectness ⊕⊖⊖⊖ VERY LOW (General- and high-risk population estimates)[a-c] due to indirectness and imprecision	general- or high-risk populations may make little to no difference in risk of all cause PID (general risk: 0.3 more in 1000 [7.6 fewer to 11 more]; high-risk: 0.5 more in 1000 [13.1 fewer to 18.7 more]), but the evidence is uncertain.
		27 per 1000	27.3 per 1000 (19.4 to 38)	0.3 more in 1000 (7.6 fewer to 11 more)		
		High-risk population‡				
		47 per 1000	47.5 per 1000 (33.9 to 65.7)	0.5 more in 1000 (13.1 fewer to 18.7 more)		
Scholes et al. – Offer to screen, selected participants						
All-cause PID (Eligible selected participants) Follow-up: 12 mos 2,607 18-34 yrs (1 RCT)	0.43 (0.21 to 0.89)	Control event rate (21 per 1000)			⊕⊕⊖⊖—⊕⊕⊕⊖ LOW-TO-MODERATE (General risk population) [d-h] due to some risk of bias and serious imprecision ⊕⊕⊖⊖ LOW (High-risk populations) [c, e-h] due to some risk of bias and indirectness, and serious imprecision	Offering a single CT screen to select groups of females 18-34 years old in general-risk populations may reduce all-cause PID (15.4 fewer per 1000 [3 to 21.3 fewer]; NNS 65 [47 to 333]). The reduction in PID may be larger for those in populations at high-risk for CT, but the magnitude of the difference is uncertain.
		21 per 1000	9.2 per 1000 (4.7 to 18.7)	11.8 fewer per 1000 (2.3 to 16.3 fewer)		
		General-risk population†				
		27 per 1000	11.6 per 1000 (5.7 to 24)	15.4 fewer per 1000 (3 to 21.3 fewer)		
		High-risk population‡				
		47 per 1000	20.2 per 1000 (9.9 to 41.8)	26.8 fewer per 1000 (5.2 to 37.1 fewer)		

*The absolute effect (and its 95% CI) without screening (i.e. baseline rate) is based on the estimated risk in the comparison group; the effect with a single screen is based on applying the relative effect of the intervention (and its 95% CI) to the effect without screening.
†The effects without screening for the general-risk population assumed that approximately 6% of the female population would have CT (prevalence), and that about 13% of these females would develop PID (0.78%), and that approximately 25-30% of all-cause PID is attributed to CT (all cause PID = 3.5 times PID from CT); 0.78% x 3.5 = 2.7%.
‡The absolute effects for the high-risk population assumed a higher (12%) CT prevalence and slightly higher (33%) attribution to CT (1.56% x 3 =4.7%). The certainty in this estimate is low because of the need to apply both the baseline rates of PID (from natural history parameters) and the effectiveness of screening from data on largely general-risk populations to high-risk populations where other factors (e.g., immunocompromised, re-infection rates, higher STI co-infection) may be important.

Explanations:
[a] Indirectness: Serious concerns about lack of PID ascertainment (Andersen used hospital diagnoses and doxycycline prescriptions; Hocking only used clinic charts; PID assessed in some ineligible [i.e. not sexually active] individuals), and use of usual care (rather than no screening) comparisons which may have underestimated the effects
[b] Imprecision: Sample size adequate but 95% CIs cross both benefit (2.5 fewer) and harm (2.5 more) thresholds
[c] Indirectness of high-risk estimate: Added concerns about using RR and natural history data from studies in general-risk population to estimate the effects of screening in high-risk populations
[d] Imprecision: Sample size adequate but entire 95% CI does not surpass the threshold.
[e] Risk of bias: Some concerns about unclear ROB for selection, performance, and detection biases.
[f] Inconsistency: Only study in analysis but findings are similar to those form a patient perspective and this study had fairly high rates of acceptance to the screening
[g] Indirectness: Use of usual care control group (rather than no screening) that would have undergone some degree of testing in asymptomatic cases, but did not rate down because believe that this would have dampened the effects such the true effect with a no screening control would still surpass the MID threshold; outcome ascertainment and applicability of setting is good in this study.
[h] Imprecision: 95% CI indicates benefit but sample size is small for rare outcome.

Screening vs. no screening; Pelvic Inflammatory Disease (Acceptors of screening)

Included studies: Ostergaard 2000 (RCT), Oakeshott 2010 (RCT), Clark 2001 (CCT); Sufrin 2012 and Low 2006 (cohort studies)
Threshold for important effect: 2.5 per 1000 fewer [benefit] or more [harm]

Trials

Outcome No. participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)*			Certainty of the evidence (GRADE)	What happens?
		Without screening	With a single CT screen	Difference		
Acceptors of screening						
All-cause PID (Trials) Follow-up: 12-18 mos 30,652 (2 RCTs, 1 CCT)	0.79 (0.60 to 1.04)	Median control event rate (18 per 1000)			⨁⨁⊖⊖ LOW (General-risk populations) due to indirectness and imprecision[a-c] ⨁⊖⊖⊖-⨁⨁⊖⊖ VERY LOW-TO-LOW (High-risk populations) due to (more) indirectness, and imprecision[a-c]	Females 15-29 years of age in general-risk populations who undergo one CT screen may have a reduced risk for PID (5.7 fewer per 1000 [10.8 fewer to 1.1 more]; NNS 75 [CI not estimable]). The benefits may be greater for those in populations at high-risk for CT, but the magnitude of the difference is uncertain.
		18 per 1000	14.3 per 1000 (10.9 to 18.7)	3.7 fewer per 1000 (7.1 fewer to 0.7 more)		
		General-risk population (27 per 1000)†				
		27 per 1000	21.3 per 1000 (16.2 to 28.1)	5.7 fewer per 1000 (10.8 fewer to 1.1 more)		
		High-risk population (47 per 1000)‡				
		47 per 1000	37.1 per 1000 (28.2 to 48.9)	9.9 fewer per 1000 (18.8 fewer to 1.9 more)		

CI: confidence interval; CTT: controlled clinical trial; PID: pelvic inflammatory disease; RCT: randomized controlled trial; ROB: risk of bias

*The absolute effect (and its 95% CI) without screening (i.e. baseline rate) is based on the estimated risk in the comparison group; the effect with a single screen is based on applying the relative effect of the intervention (and its 95% CI) to the effect without screening.
†The effects without screening for the general-risk population assumed that approximately 6% of the female population would have CT (prevalence), and that about 13% of these females would develop PID (0.78%), and that approximately 25-30% of all-cause PID is attributed to CT (all cause PID = 3.5 times PID from CT); 0.78% x 3.5 = 2.7%.
‡The absolute effects for the high-risk population assumed a higher (12%) CT prevalence and slightly higher (33%) attribution to CT (1.56% x 3 =4.7%). The certainty in this estimate is low because of the need to apply both the baseline rates of PID (from natural history parameters) and the effectiveness of screening from data on largely general-risk populations to high-risk populations where other factors (e.g., immunocompromised, re-infection rates, higher STI co-infection) may be important.

Explanations:

[a] Some concerns in Clark (selection bias) and Ostergaard (incomplete outcome data; use of complete case analysis with 47% follow-up) but point estimate quite consistent with those from low ROB trial Oakeshott, and Ostergaard contributes very little weight (5%) in analysis so did not rate down.

[b] Serious concerns about applicability of settings (outreach) to primary care in all three trials and possibly low ascertainment of PID (Clark used hospital diagnoses only; Ostergaard used self-report). The use of usual care rather than no screening comparators may have dampened the effects, but the true effect with a no screening control would still surpass the MID threshold so did not rate down. We also assessed the certainty specific to an outreach setting which led to less uncertainty (-1.0 versus -1.5). For the high-risk population estimate of a small-to-moderate effect, we have additional uncertainty because of reliance on the RR and baseline estimates of PID that were generated from data in general-risk populations

[c] Adequate sample size but large portion of 95% CI does not cross the MID threshold

Screening vs. no screening; Ectopic Pregnancy

Included studies: Offer to screen, regardless of uptake: Andersen 2011 (RCT); Acceptors of screening: Clark 2001 (CCT), Low 2006 (cohort)
Threshold for important effect: 1 per 1000 fewer [benefit] or more [harm]

Outcome No. participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)*			Certainty of the evidence (GRADE)	What happens?
		Without screening	With a single CT screen	Difference		
Offer to screen - All eligible participants (based on age and sexual activity), regardless of uptake						
Ectopic pregnancy (general risk) Follow-up: 9 yrs 15,459 (1 RCT)	RR 1.03 (0.67 to 1.60)	6.5 per 1000	6.35 per 1000 (4.4 to 10.5)	0.20 more per 1000 (2.2 fewer to 3.9 more)	⨁⊖⊖⊖ VERY LOW for concerns about lack of consistency and indirectness and serious concerns about imprecision[a-c]	Offering a single CT screen to general-risk females may make little to no difference in rates of ectopic pregnancy (0.20 more in 1000 [2.2 fewer to 3.9 more]), but the evidence is very uncertain.
Acceptors of screening						
Ectopic pregnancy (high risk) Follow-up: 3 yrs 28,074 (1 CCT)	RR 1.19 (0.77 to 1.85)	3.3 per 1000	4.0 per 1000 (2.6 to 6.2)	0.63 more per 1000 (0.76 fewer to 2.8 more)	⨁⊖⊖⊖ VERY LOW for concerns about risk of bias and imprecision and very serious concerns about indirectness[d-g]	For females who attend a single screen for CT, there may be little to no difference in rates of ectopic pregnancy (0.63 more per 1000 [0.76 fewer to 2.8 more]), but the evidence is very uncertain.

CI: confidence interval; CT: chlamydia trachomatis; CCT: controlled clinical trial; OR: odds ratio; RCT: randomized controlled trial

*The effect with screening (and its 95% confidence interval) is based on the effects without screening and the relative effect of the intervention (and its 95% CI).

Explanations:

[a] Concern about lack of evidence of consistency.

[b] Concern about indirectness from poor outcome ascertainment (only hospital diagnoses) and use of usual care comparison group.

[c] Serious concern about imprecision because 95% CI of absolute effects crosses thresholds for benefits and harms.
[d] Concern about ROB from selection bias.
[e] Some concerns about lack of evidence of consistency but results are similar between CTT and observational study.
[f] Very serious concern about indirectness from poor outcome ascertainment (only hospital diagnoses), use of usual care comparison group, setting being inapplicable to primary care, and having limited follow-up duration (3 yrs)
[g] Concern about imprecision because 95% CI of absolute effects crosses threshold for harm.

Screening vs. no screening; Infertility

Included studies: Offer to screen, regardless of uptake: Andersen 2011 (RCT); Acceptors of screening: Clark 2001 (CCT), Low 2006 (cohort)
Threshold for important effect: 1 per 1000 fewer [benefit] or more [harm]

Outcome No. participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)*			Certainty of the evidence (GRADE)	What happens?
		Without screening	With a single CT screen	Difference		
Offer to screen – All eligible participants (based on age and sexual activity), regardless of uptake						
Infertility (general-risk females) Follow-up: 9 years 15,459 (1 RCT)	RR 1.15 (0.94 to 1.40)	28.1 per 1000	32.3 per 1000 (26.4 to 39.3)	4.2 more per 1000 (1.7 fewer to 11.2 more)	⊕⊖⊖⊖ VERY LOW due to lack of consistency, indirectness and imprecision[a-c]	The evidence is very uncertain about the effects on infertility from offering a single CT screen to general-risk females.
Acceptors of screening						
Infertility (high-risk females) Follow-up: 1.5 years 28,074 (1 CCT)	RR 0.66 (0.14 to 3.06)	0.43 per 1000	0.28 per 1000 (0.06 to 1.31)	0.15 fewer per 1000 (0.37 fewer to 0.88 more)	⊕⊖⊖⊖ VERY LOW due to ROB, inconsistency and indirectness[d-f]	The evidence is very uncertain about the effects on infertility for general-risk females who undertake a single CT screen.

CI: confidence interval; CT: chlamydia trachomatis; CCT: controlled clinical trial; OR: odds ratio; RCT: randomized controlled trial

*The effect with a single CT screen (and its 95% confidence interval) is based on the effect without screening and the relative effect of the intervention (and its 95% CI).

Explanations:

[a] Concerns about lack of evidence of consistency.
[b] Serious concerns about outcome ascertainment (hospital diagnoses) and use of usual care comparison group.
[c] Sample size may be adequate but 95% CI crosses thresholds for benefit and harm (1 fewer and 1 more per 1000, respectively)
[d] Concerns about ROB from selection bias
[e] Some concerns that only study in analysis but findings are consistent between CCT and observational study

[f] Very serious concern about indirectness from poor outcome ascertainment (only hospital diagnoses), use of usual care comparison group, setting being inapplicable to primary care, and having limited follow-up duration (3 yrs)

Screening offer vs. no screening; Transmission of CT: Population prevalence (Offer to screen, regardless of uptake)

Included studies: RCTs van den Broek, Hocking, Hodgins, Garcia, CCT: Cohen
Thresholds for important effect (MID): 5 or 10 per 1000 fewer [benefit] or more [harm]

Outcome No. participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)*			Certainty of the evidence (GRADE)	What happens?
		Without screening	With a single CT screen	Difference		
Transmission: estimated population prevalence of CT (Both sexes in general-risk population) Follow-up: 12-36 mos 41,709 (3 cluster RCTs)	RR: 0.91 (0.65 to1.21)	33 per 1000	30 per 1000 (21.5 to 39.93)	3 fewer per 1000 (11.5 fewer to 6.9 more)	⨁⨁◯◯ LOW (0.5% MID) ⨁⨁⨁◯-⨁⨁◯◯ MODERATE-TO-LOW (1% MID)	Screening both sexes, 15-29 years old at general-risk, for CT annually may make little to no difference in the prevalence of CT.

CI: confidence interval; CT: chlamydia trachomatis; CCT: controlled clinical trial; MID: minimally important difference; NG: neisseria gonorrhea; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; ROB: risk of bias

Explanations:
Both sexes in general population; low-intensity CT screening for females and males: for all three trials there was some concern about **ROB** from performance bias and attrition bias, Hodgins and van den Broek were also unclear for detection bias**;** concerns about **indirectness** because of the use of usual care (rather than no screening) for the control groups which may have underestimated the effects from screening**; imprecision** around the finding of little to no difference is serious, with the range of effects indicating possible benefit. There is more certainty that the true effect will not meet an importance threshold of 10 fewer in 1000.

1UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small **X Little to no difference** ○ Varies ○ Don't know	# Anticipated undesirable effects (Harms) One RCT (n=37,543 tested; n=4,574 with CT diagnosis; number treated not reported) reported no adverse events from antibiotic treatment for CT (very low certainty evidence) (3). Ten cohort studies reported on a variety of psychosocial harms of screening (33-42). Low- or very low-certainty evidence indicated that undergoing screening may lead to symptoms of stigmatization (e.g., guilt, embarrassment, social disapproval) or feelings of anxiety about one's future infertility, sexuality, or risk of infection in a small to moderate proportion of individuals (50-400 per 1,000 individuals screened) (32). The duration and severity of these effects is unknown. Note that all studies related to harm examined individuals undergoing screening, and thus, the extent of those affected would be lower for an entire population of individuals eligible for screening. No studies examined the harms of screening for NG. Task Force members and KT patient focus groups did not rate harms from screening or treatment as critical to screening decision-making (rated as important) (43,44). ## Judgment **The Task Force judged that screening is anticipated to have little to no impact on harms.** This is based on the very uncertain evidence of no reported adverse events from antibiotic treatment, and uncertain evidence for psychosocial harms of screening that are likely to be experienced by a small proportion of those eligible for screening.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** **X Very low** ○ Low ○ Moderate ○ High ○ No included studies	# Certainty ## Judgment There is overall ***very low certainty*** evidence for an effect of screening for chlamydia and gonorrhea for the critical outcomes of interest in sexually active individuals. This is due to the very uncertain or lack of evidence for some critical outcomes for CT, and for all outcomes of interest for NG. In addition, the indirectness (low applicability) of available evidence to inform opportunistic screening in Canada, as outlined in the benefits section, represents a major source of uncertainty for the guideline.
VALUES	**Is there important uncertainty about or variability in**	# Values

	how much people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability **X Probably no important uncertainty or variability** ○ No important uncertainty or variability	**Evidence considering benefits and harms** **Surveys and qualitative studies** Considering benefits relative to harms, surveys and qualitative studies found that individuals considering screening (n=777) (45-51) or undergoing screening (n=77) (52-54) placed greater relative importance on potential reproductive health and transmission benefits compared to anxiety or stigma of screening (very low-certainty evidence). No studies considered adverse events from medication. **Patient engagement** The task force patient engagement study indicated that patients likely prioritize potential benefits of screening (all rated important or critical) over harms (all rated important) and have a strong preference to be screened; this was the case even when participants were presented with the evidence and its uncertainty (43,44). **Evidence considering benefits only** **Health state utility studies** Considering the relative prioritization of different screening benefits, studies reporting health state utilities found that utility values are similar across benefit outcomes (9,55-57), when considering durations of the health states, the avoidance of infertility and chronic pelvic pain may be more important to females than ectopic pregnancy, PID, or cervicitis (low-to-moderate certainty) (32). **Judgment:** The judgment of the Task Force is that most Canadian patients prioritize the benefits over the harms of screening for CT and NG, even when provided with the evidence and its uncertainty.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison X **Probably favors the intervention** ○ Favors the intervention	# Balance of effects ## Judgment The judgment of the Task Force is that the balance of benefits and harms probably favours opportunistic screening for CT and NG for sexually active individuals under 30 years of age, and not known to belong to a high risk group, given: • Uncertain evidence for a small but potentially important benefit to reduce PID in females. Evidence in males is lacking, but they serve as a reservoir for transmission to females. • Little to no difference in harms, that impact a small proportion of those eligible for screening. • Canadian patients likely prioritize benefits over harms, even when provided with the evidence and its uncertainty • Despite the lack of available evidence on NG, like CT, many NG cases are asymptomatic and identified only through screening. Additionally, up to 40% of those with NG may have CT (29-31).
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs X **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	# Resources required A systematic review was not conducted on resource use or cost-effectiveness. ## Judgment In the judgement of the task force, the recommendation to screen all eligible patients at opportunistic visits could represent moderate costs, largely due to clinician time and testing costs. The incremental costs of screening for both CT and NG (versus, for example, CT alone) is uncertain, as many provincial schedules include NAAT for CT and NG under a single price (58,59).

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** **X Very low** ○ Low ○ Moderate ○ High	# Certainty of resources required **Judgment** There are therefore uncertainties regarding the resources required for screening.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention **X Varies**	# Cost Effectiveness A full systematic review on cost-effectiveness was not carried out. Cost-effectiveness estimates based on opportunistic screening scenarios suggest that high versus low rates of screening may improve cost-effectiveness (60), and that screening may be cost-effective in Canada provided that the probability of chlamydia progressing to PID is at least 10% (61), although this is of very low certainty. This evidence is very uncertain due to input assumptions. **Judgment** In the judgment of the Task Force, cost-effectiveness varies depending on screening rates, and may favour screening for CT and screening rates are higher (50-75%) rather than lower (10-30%).
EQUITY	**What would be the impact on health equity? (for recommendation in favour)** ○ Reduced ○ Probably	# Equity This recommendation to routinely offer screening to all sexually active individuals (under 30 years) who are not known to belong to a high risk group, could improve equity through normalization as routine for sexually active individuals and thereby reducing important barriers to screening, such as fear of disapproval or discrimination and feelings of stigmatization (62). This recommendation applies to all sexually active individuals regardless of sexual orientation and considered a broad definition of

	reduced ○ Probably no impact **X Probably increases** ○ Increased ○ Varies ○ Don't know	sexual activity. Additionally, since females carry most of the burden of clinical consequences of infection, screening of males (a reservoir of infection for females) may improve health equity for females. **Judgment** In the judgment of the task force, a recommendation in favour of opportunistic screening for CT and NG would likely improve health equity.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders? (for recommendation in favour)** ○ No ○ Probably no **X Probably yes** ○ Yes ○ Varies ○ Don't know	**Acceptability** **Primary Care Clinicians:** Screening for CT and NG is familiar to primary care clinicians as it is part of current practice. **Patients:** Screening strategies that are less invasive (urine samples, self-collected vaginal swabs) are likely to be acceptable to patients. One included RCT reported screening was accepted 80% of the time that it was offered (although the overall screening rate was low due to lack of offer) (63). **Health policy-makers:** Public health policy-makers are anticipated to find the recommendation to screen acceptable given the number of people affected, increasing incidence of CT and NG infection (2), and availability of effective treatment. **Judgment** In the judgment of the Task Force, a recommendation in favor of opportunistic screening, especially if via less invasive methods (i.e. urine samples and vaginal self-swabs) would probably be acceptable to most key stakeholders.
FEASIBILITY	**Is the intervention feasible to implement? (for recommendation in favour)** ○ No ○ Probably no **X Probably yes** ○ Yes	**Feasibility** **Primary Care Clinicians** Screening for CT and NG is already a standard part of primary care practice in Canada. Current Canadian clinical and laboratory practice is to combine testing for CT and NG using a single sample; most commercial NAAT assays test for both organisms simultaneously with a single specimen (27). **Patients**

	○ Varies ○ Don't know	The availability non-invasive sample collection methods and combined testing for CT and NG with a single sample contributes to convenience for patients. **Health policy-makers** Screening for CT and NG is currently recommended in national guidance (16). Cost and resources of scaling up and sustainability of screening are considerations for feasibility. **Judgment:** In the judgment of the Task Force, a recommendation in favour of opportunistically screening sexually active individuals under 30 years of age who are not known to belong to a high risk group, for chlamydia and gonorrhea at primary care visits, would probably be feasible.

Summary of judgments

	JUDGMENT					
PROBLEM	No	Probably no	Probably yes	**Yes**	Varies	Don't know
DESIRABLE EFFECTS	Little to no	**Small**	Moderate	Large	Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Little to no**	Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High	No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability		

	JUDGMENT					
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High	No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased (for recommendation in favour)**	Increased	Varies
ACCEPTABILITY	No	Probably no	**Probably yes (for recommendation in favour)**	Yes	Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes (for recommendation in either direction)**	Yes	Varies	Don't know

Conclusions

Should [intervention] vs. [comparison] be used for [health problem and/or population]?

TYPE OF RECOMMENDATION	Strong recommendation	Conditional recommendation	Conditional recommendation for either the	**Conditional recommendation for the intervention**	Strong recommendation for the intervention

Appendix 3 (as supplied by the authors). Appendix to: Moore A, Traversy G, Reynolds DL, et al; for the Canadian Task Force on Preventive Health Care. Recommendation on screening for chlamydia and gonorrhea in primary care for individuals not known to be at high risk. *CMAJ* 2021. doi: 10.1503/cmaj.201967.

	against the intervention ○	against the intervention ○	intervention or the comparison ○	**X**	○
RECOMMENDATION	We recommend opportunistic screening of sexually active individuals under 30 years of age who are not known to belong to a high-risk group for chlamydia and gonorrhea at primary care visits, using a self- or clinician-collected sample (Conditional recommendation; very low-certainty evidence).				
JUSTIFICATION	**Benefits** The indirectness (low applicability) of available evidence to inform opportunistic screening in Canada represents a major source of uncertainty, in addition to the very uncertain or lack of evidence for some outcomes of interest for CT and for all outcomes of interest for NG. All evidence on benefits was of low or very low certainty, largely due to concerns about such indirectness as well as imprecision (Appendix 1). PID may be reduced for those accepting and undergoing screening (6,19,24) and for those interested in being screened (low certainty) (22). Very uncertain evidence found little to no difference in PID when CT screening was offered via mailed invitation or clinic-level packages encouraging screening (regardless of uptake). The task force judged that the true benefit of CT screening when offered in person by Canadian primary care practitioners, who are positioned to identify those eligible and offer screening opportunistically, would likely lie within this observed range of screening effectiveness. There was insufficient evidence to develop individualized screening recommendations for specific high-risk populations. Almost all evidence of benefit was from studies of individuals under 30 years of age (32). This recommendation to also screen sexually active males is intended to reduce CT and NG infection and its negative consequences in females, through their role in the transmission of these infections (although there were no available studies informing this rationale). The recommendation to also screen for NG was made (despite the lack of available evidence) given that current Canadian clinical and laboratory practice is to combine testing for NG with CT using a single sample, and most commercial NAAT assays test for both organisms simultaneously with a single specimen (27). Also, as with CT, many NG cases are asymptomatic (17,28) and identified only through screening. Additionally, up to 40% of those with NG may have CT (29-31). **Harms** The task force placed a lower priority on the very uncertain evidence of no serious adverse effects of antibiotic treatment for CT and NG and uncertain evidence for psychosocial harms of screening (anxiety, shame and stigma) that are likely to be experienced by a small proportion of those eligible for screening. The potential benefits of screening for CT and NG to reduce PID in females, albeit very uncertain, were judged to outweigh possible harms. Evidence suggests that most Canadian patients also prioritize the benefits over the harms of screening for CT and NG, even when provided with the evidence and its uncertainty (43,44). Therefore, considering the balance of benefits and harms as well as evidence uncertainty, the task force provides a conditional recommendation in favour of opportunistic screening for CT and NG in primary care.				

SUBGROUP CONSIDERATIONS	A number of subgroups were sought but sufficient evidence was unavailable to develop recommendations on CT / NG screening focused to specific groups who may be at increased risk based on sexual behaviours and/or other factors (e.g., geography, membership in a vulnerable group, high-risk sexual behaviours, and biological and epidemiological factors).
IMPLEMENTATION CONSIDERATIONS	• To implement this screening recommendation, clinicians in primary care settings are advised to identify individuals who are eligible for screening (sexually active individuals under 30 years of age), not seeking testing for a possible STI, and to offer CT and NG screening opportunistically (i.e., without requiring a separate screening visit, and not only during sexual health visits). • As individuals at high risk of CT and NG infection may not always readily self-identify or be easily identified by clinicians, this routine offer of screening applies to all sexually active individuals without clinician knowledge of their membership of a high-risk group. Sexually transmitted infections are associated with shame, embarrassment and significant stigma, which could prevent patients from seeking screening and treatment (62,64). Routinely offering screening to all sexually active individuals has been suggested as one way to reduce stigma associated with testing for STIs (64). • Informed consent is required for STI testing; address privacy, reporting of positive test results to local public health offices and potential partner notification. • Annual screening may be appropriate for general risk individuals (though optimal screening interval unknown) • Minimally invasive sample collection methods may improve acceptability and uptake (65-67), (self-collected vaginal swabs from females and urine samples from males are the most accurate (NAAT) (68)). • Clinician-collected swabs are likely acceptable and feasible during certain encounters (e.g. Pap testing). • Local, provincial and territorial authorities (public health offices, child protection services, pediatricians and clinical experts) as available and appropriate, for STI testing, treatment, reporting and management of actual or suspected child sexual abuse. • Consider pharyngeal and rectal swabs as deemed to be clinically warranted.
MONITORING AND EVALUATION	Rates of offer and uptake of screening among patients in primary care settings are a key performance measure for this guideline. Rates of reported CT and NG infections represent another performance metric.
RESEARCH PRIORITIES	We did not identify any trials that carried out screening for CT or NG in a manner consistent with how screening is offered directly to patients, opportunistically, in Canadian primary care. There was also limited evidence on health outcomes of screening for chlamydia or gonorrhea in men or their specific female partners (considering sexual networks). Studies comparing different screening intervals in primary care settings would be informative.

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