Estimating the lifetime risk of a false positive screening test result

Supplementary material

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Table S1: Inclusion criteria for each disease

Disease	Date of most recent USPSTF screening recommendation as of August 31, 2021	Cancer, STD, or neither	USPSTF grade of C or higher for at least some individuals	Included in analysis
Breast cancer	February 2016 ¹	Cancer ²	Yes ¹	Yes
Cervical cancer	August 2018 ³	Cancer ²	Yes^3	Yes
Chlamydia	December 2014 ⁴	STD^5	Yes ⁴	Yes
Colorectal cancer	May 2021 ⁶	Cancer ²	Yes ⁶	Yes
Gonorrhea	December 2014 ⁴	STD^5	Yes ⁴	Yes
Hepatitis B	December 2020^7 and July 2019^8	STD^5	7,8	Yes
Hepatitis C	March 2020 ⁹	STD^5	Yes ⁹	Yes
HIV	June 2019 ¹⁰	STD^5	Yes^{10}	Yes
Lung cancer	March 2021 ¹¹	Cancer ²	Yes^{11}	Yes
Prostate cancer	May 2018^{12}	Cancer ²	Yes^{12}	Yes
Syphilis	June 2016^{13} and September 2018^{14}	STD^5	$\mathrm{Yes}^{13,14}$	Yes
Abdominal aortic aneurysm	December 2019 ¹⁵	Neither ^{2,5}	Yes^{15}	No
Asymptomatic bacteriuria	September 2019 ¹⁶	Neither ^{2,5}	$ m Yes^{16}$	No
Bladder cancer	August 2011 ¹⁷	Cancer ²	No^{17}	No
Depression	March 2016^{18} and January 2016^{19}	Neither 2,5	$Yes^{18,19}$	No
Genital herpes	December 2016 ²⁰	STD^5	No^{20}	No
Gestational diabetes	August 2021 ²¹	Neither ^{2,5}	Yes^{21}	No
Hypertension	April 2021 ²²	Neither ^{2,5}	Yes^{22}	No

Intimate partner violence, elder abuse, and abuse of vulnerable adults	October 2018^{23}	Neither 2,5	Yes^{23}	No
Latent tuberculosis	September 2016 ²⁴	Neither ^{2,5}	Yes^{24}	No
Oral cancer	January 2014 ²⁵	Cancer ²	No^{25}	No
Osteoporosis	June 2018 ²⁶	Neither ^{2,5}	Yes^{26}	No
Ovarian cancer	February 2018 ²⁷	Cancer ²	No^{27}	No
Pancreatic cancer	August 2019 ²⁸	Cancer^2	No^{28}	No
Prediabetes and type 2 diabetes	August 2021 ²⁹	Neither 2,5	Yes^{29}	No
Preeclampsia	April 2017 ³⁰	Neither ^{2,5}	Yes^{30}	No
Rh(D) incompatibility	February 2004 ³¹	Neither ^{2,5}	Yes^{31}	No
Skin cancer	July 2016 ³²	Cancer ²	No^{32}	No
Testicular cancer	April 2011 ³³	Cancer ²	No^{33}	No
Thyroid cancer	May 2017 ³⁴	Cancer ²	No^{34}	No
Unhealthy drug use	June 2020 ³⁵	Neither ^{2,5}	Yes^{35}	No
Vision in children	September 2017 ³⁶	Neither ^{2,5}	Yes^{36}	No

Note: The diseases listed in this table are those that satisfy one or both of the inclusion criteria defined in Section 2.1 of the manuscript — i.e., (1) the disease must be a cancer or an STD and (2) the USPSTF must have assigned a grade of C or higher to the screening service for the disease for at least some individuals.

Table S2: Lifetime number of screening occasions for each disease by subpopulation

$Female\ subpopulations$

Disease	Screening procedure	FB FP1		FP2	\mathbf{FS}	FSP1	FSP2
Breast cancer	Mammogram	13	13	13	13	13	13
Cervical cancer	Pap test	15	15	15	15	15	15
Chlamydia	NAAT	4	4	4	4	4	4
Colorectal cancer	Colonoscopy	4	4	4	4	4	4
Gonorrhea	NAAT	4	4	4	4	4	4
Hepatitis B	HBsAg test	0	1	2	0	1	2
Hepatitis C	Anti-HCV antibody test	1	2	3	1	2	3
HIV	Antigen/antibody test	1 2		3	1	2	3
Lung cancer	Low-dose CT scan	0	0	0	1	1	1
Prostate cancer	PSA test	0	0	0	0	0	0
Syphilis	RPR test	0	1	2	0	1	2
Key: FB	$Baseline\ females$		FS	Female :	smoker	rs	
FP1	Females, one pregnancy	\boldsymbol{F}	SP1	Female :	smoker	rs, one pr	egnancy
FP2	Females, two pregnancies	FSP2		Female :	smoker	rs, two pr	egnancies

$Male\ subpopulations$

Disease	Screening procedure	MB	MSM	MS	MSMS	MP	MSMP	MPS	MSMPS
Breast cancer	Mammogram	0	0	0	0	0	0	0	0
Cervical cancer	Pap test	0	0	0	0	0	0	0	0
Chlamydia	NAAT	0	6	0	6	0	6	0	6
Colorectal cancer	Colonoscopy	4	4	4	4	4	4	4	4
Gonorrhea	NAAT	0	6	0	6	0	6	0	6
Hepatitis B	HBsAg test	0	0	0	0	0	0	0	0
Hepatitis C	Anti-HCV antibody test	1	1	1	1	1	1	1	1
HIV	Antigen/antibody test	1	6	1	6	1	6	1	6
Lung cancer	Low-dose CT scan	0	0	1	1	0	0	1	1
Prostate cancer	PSA test	0	0	0	0	8	8	8	8
Syphilis	RPR test	0	6	0	6	0	6	0	6

Key:	MB	Baseline males	MP	Males, routine prostate exams
	MSM	Men who have sex with men	MSMP	MSM, routine prostate exams
	MS	Male smokers	MPS	Male smokers, routine prostate exams
	MSMS	$MSM\ smokers$	MSMPS	MSM smokers, routine prostate exams

Table S3: Data collection procedure for each disease

Disease	Data collection procedure
Breast cancer	2016 USPSTF recommendation statement $^1 \rightarrow 2002$ USPSTF evidence summary $^{37} \rightarrow$ Mushlin et al 1998 38 (Malmo, Swedish Two-County) \rightarrow Baines et al 1988 39 (Canadian), Frisell et al 1986 40 (Stockholm)
Cervical cancer	2018 USPSTF recommendation statement $^3 \rightarrow 2018$ USPSTF evidence review 41 (ARTISTIC round 1, ARTISTIC round 2, FINNISH, NTCC phase I, NTCC phase II, POBASCAM round 1, POBASCAM round 2, SWEDESCREEN)
Chlamydia	2014 USPSTF recommendation statement $^4 \rightarrow 2014$ USPSTF evidence review 42 (Chernesky 2005, Gaydos 2013, Schacter 2003, Schoeman 2012, Shrier 2004, Taylor 2011, Taylor 2012, Van Der Pol 2012a)
Colorectal cancer	2021 USPSTF recommendation $^6 \rightarrow$ 2021 USPSTF evidence review 43 (Zalis 2012)
Gonorrhea	2014 USPSTF recommendation statement $^4 \rightarrow 2014$ USPSTF evidence review 42 (Chernesky 2005, Gaydos 2013, Stewart 2012, Taylor 2012, Van Der Pol 2012a, Van Der Pol 2012b)
Hepatitis B	2020 USPSTF recommendation statement $^7 \rightarrow 2009$ USPSTF reaffirmation recommendation statement $^{44} \rightarrow 2004$ USPSTF recommendation statement $^{45} \rightarrow 2004$ USPSTF evidence review $^{46} \rightarrow 1996$ USPSTF recommendation statement $^{47} \rightarrow$ McCready et al 1991^{48} (McCready 1991), Toplikar et al 1993^{49} (Toplikar 1993)
Hepatitis C	2020 USPSTF recommendation statement $^9 \rightarrow 2013$ USPSTF recommendation statement $^{50} \rightarrow 2004$ USPSTF recommendation statement $^{51} \rightarrow 2004$ USPSTF evidence review 52 (Huber 1996, Prince 1997) \rightarrow Colin et al 2001^{53} (Couroucé 1994, Janot 1994, Lavanchy 1996, Stuyver 1996)
HIV	2019 USPSTF recommendation statement $^{10} \rightarrow$ Branson et al 2014 54 (Bentsen 2011, Chavez 2011, Dubravac 2013, Masciotra 2011, Nasrullah 2013, Product insert 2010, Product insert 2011)
Lung cancer	2021 USPSTF recommendation statement $^{11} \rightarrow 2021$ USPSTF evidence review 55 (Becker 2015, De Koning 2020, Infante 2015, Lopes Pegna 2013, Pinsky 2013, Sverzellati 2016)
	2018 USPSTF recommendation statement $^{12} \rightarrow 2018$ USPSTF evidence review $^{56} \rightarrow 2012$ USPSTF recommendation statement $^{57} \rightarrow 2011$ USPSTF evidence review $^{58} \rightarrow 2008$ USPSTF recommendation statement $^{59} \rightarrow Gann$ et al 1995 (Gann 1995)
Prostate cancer	2008 USPSTF evidence update $^{61} \rightarrow 2002$ USPSTF recommendation statement $^{62} \rightarrow 2002$ USPSTF evidence update $^{63} \rightarrow$ Mettlin et al 1996 (Mettlin 1996), Jacobsen et al 1996 (Jacobsen 1996)
Syphilis	2016 USPSTF recommendation statement (nonpregnant adults and adolescents) ¹³ \rightarrow 2016 USPSTF evidence review (nonpregnant adults and adolescents) ⁶⁶ \rightarrow Ratnam 2005 ⁶⁷ \rightarrow Larsen et al 1998 ⁶⁸ \rightarrow Pettit et al 1983 ⁶⁹ (Pettit 1983)
зурпшs	2018 USPSTF recommendation statement (pregnant women) $^{14} \rightarrow 2018$ USPSTF evidence review (pregnant women) $^{70} \rightarrow$ Wang et al 2016^{71} (Wang 2016), Liu et al 2014^{72} (Liu 2014)
	Note: Bold text denotes the study IDs from the data set. ⁷³

Table S4: Estimated lifetime false positive probability by subpopulation, cancers only and STDs only

	$Cancers\ only$	$STDs \ only$
Subpopulation	Estimate (SE)	Estimate (SE)
Baseline females	85.0% (0.9%)	3.9%~(0.2%)
Females, one pregnancy	85.0% (0.9%)	7.3% (0.4%)
Females, two pregnancies	85.0% (0.9%)	10.5% (0.5%)
Female smokers	88.1% (0.7%)	3.9%~(0.2%)
Female smokers, one pregnancy	88.1% (0.7%)	7.3% (0.4%)
Female smokers, two pregnancies	88.1% (0.7%)	$10.5\% \ (0.5\%)$
Baseline males	38.2% (3.7%)	1.2% (0.2%)
Men who have sex with men (MSM)	38.2% (3.7%)	8.0% (0.3%)
Male smokers	50.9% (2.9%)	1.2% (0.2%)
MSM smokers	50.9% (2.9%)	8.0% (0.3%)
Males, routine prostate exams	73.9% (1.7%)	1.2% (0.2%)
MSM, routine prostate exams	73.9% (1.7%)	8.0% (0.3%)
Male smokers, routine prostate exams	79.3% (1.3%)	1.2% (0.2%)
MSM smokers, routine prostate exams	79.3% (1.3%)	8.0% (0.3%)

Table S5: Estimated lifetime false positive probability for each disease by subpopulation

$Female\ subpopulations$

Disease	Screening procedure	FB	FP1	FP2	FS	FSP1	FSP2
Breast cancer	Mananaamana	47.7%	47.7%	47.7%	47.7%	47.7%	47.7%
breast cancer	Mammogram	(0.4%)	(0.4%)	(0.4%)	(0.4%)	(0.4%)	(0.4%)
Cervical cancer	Don toot	53.5%	53.5%	53.5%	53.5%	53.5%	53.5%
Cervical cancer	Pap test	(0.4%)	(0.4%)	(0.4%)	(0.4%)	(0.4%)	(0.4%)
Chlamatia	NAAT	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%
Chlamydia	NAA1	(0.1%)	(0.1%)	(0.1%)	(0.1%)	(0.1%)	(0.1%)
Calamatal	C-1	38.2%	38.2%	38.2%	38.2%	38.2%	38.2%
Colorectal cancer	Colonoscopy	(3.7%)	(3.7%)	(3.7%)	(3.7%)	(3.7%)	(3.7%)
Gonorrhea	NAAT	0.8%	0.8%	0.8%	0.8%	0.8%	0.8%
	NAAT	(0.1%)	(0.1%)	(0.1%)	(0.1%)	(0.1%)	(0.1%)
	HBsAg test		2.0% 4.1%			2.0%	4.1%
Hepatitis B		X	(0.1%)	(0.3%)	X	(0.1%)	(0.3%)
Htiti- C	Anti HCV milled at an	1.0%	1.9%	2.9%	1.0%	1.9%	2.9%
Hepatitis C	Anti-HCV antibody test	(0.2%)	(0.3%)	(0.5%)	(0.2%)	(0.3%)	(0.5%)
1117	A .: / .:1 1	0.2%	0.4%	0.6%	0.2%	0.4%	0.6%
HIV	Antigen/antibody test	(<0.1%)	(<0.1%)	(0.1%)	(<0.1%)	(<0.1%)	(0.1%)
	I I CT				20.7%	20.7%	20.7%
Lung cancer	Low-dose CT scan	X	X	x	(0.1%)	(0.1%)	(0.1%)
Prostate cancer	PSA test	х	X	x	х	х	x
Combilia	DDD toot		0.3%	0.6%		0.3%	0.6%
Syphilis	RPR test	Х	(< 0.1%)	(0.1%)	Х	(< 0.1%)	(0.1%)

Key:	FB	$Baseline\ females$	FS	Female smokers
	FP1	Females, one pregnancy	FSP1	Female smokers, one pregnancy
	FP2	Females, two pregnancies	FSP2	$Female\ smokers,\ two\ pregnancies$

$Male\ subpopulations$

Disease	Screening procedure	MB	MSM	MS	MSMS	MP	MSMP	MPS	MSMPS
Breast cancer	Mammogram	х	x	х	х	х	x	x	х
Cervical cancer	Pap test	х	x	x	x	x	x	x	х
Chlamydia	NAAT	x	3.0% $(0.2%)$	x	3.0% $(0.2%)$	x	3.0% $(0.2%)$	x	3.0% (0.2%)
Colorectal cancer	Colonoscopy	38.2% $(3.7%)$	38.2% $(3.7%)$	38.2% $(3.7%)$	38.2% $(3.7%)$	38.2% $(3.7%)$	38.2% $(3.7%)$	38.2% $(3.7%)$	38.2% (3.7%)
Gonorrhea	NAAT	x	1.2% (0.2%)	x	1.2% (0.2%)	x	1.2% (0.2%)	x	1.2% (0.2%)
Hepatitis B	HBsAg test	x	x	x	x	x	x	x	х
Hepatitis C	Anti-HCV antibody test	1.0% $(0.2%)$	1.0% $(0.2%)$	1.0% $(0.2%)$	1.0% $(0.2%)$	1.0% $(0.2%)$	1.0% $(0.2%)$	1.0% $(0.2%)$	1.0% (0.2%)
HIV	Antigen/antibody test	0.2% (<0.1%)	1.2% (0.1%)	0.2% (<0.1%)	1.2% (0.1%)	0.2% (<0.1%)	1.2% (0.1%)	0.2% (<0.1%)	1.2% (0.1%)
Lung cancer	Low-dose CT scan	х	х	20.7% (0.1%)	20.7% (0.1%)	x	x	20.7% (0.1%)	20.7% (0.1%)
Prostate cancer	PSA test	x	x	x	х	57.9% (1.1%)	57.9% (1.1%)	57.9% (1.1%)	57.9% (1.1%)
Syphilis	RPR test	x	1.9% (0.2%)	x	1.9% (0.2%)	x	1.9% (0.2%)	x	1.9% (0.2%)

Key:	MB	Baseline males	MP	Males, routine prostate exams
	MSM	Men who have sex with men	MSMP	MSM, routine prostate exams
	MS	Male smokers	MPS	Male smokers, routine prostate exams
	MSMS	MSM smokers	MSMPS	MSM smokers, routine prostate exams

Section S1: Details about lifetime number of screening occasions

The number of times that individuals are recommended to get screened in a lifetime varies by subpopulation for each disease. For some diseases, it is straightforward to derive the lifetime number of screening occasions from the USPSTF guidelines. This is the case for breast cancer, as biennial mammography for women aged 50 to 74 implies 13 mammograms in a lifetime for each female subpopulation. The same is true for cervical cancer — a woman who gets screened with a Pap test every three years between the ages of 21 and 65 will receive 15 Pap tests in a lifetime. It is also true for colorectal cancer, as an individual who gets a colonoscopy every ten years between the ages of 45 and 75 will receive a lifetime total of four colonoscopies.

For other diseases, the USPSTF guidelines lack either an age range, an interval at which screening should be repeated, or both. In these ambiguous cases, we adopt a conservative approach by imposing assumptions that are more likely to underestimate, rather than overestimate, the lifetime number of screening occasions for a particular subpopulation. This approach ensures that our estimates do not overstate the lifetime risk of a false positive. In fact, for the cases described below where we adopt this conservative approach, our estimates should be interpreted as lower bounds — i.e., the lifetime probability of a false positive for these diseases is at least as high as our estimates.

Unlike the USPSTF cancer screening guidelines, the USPSTF guidelines for the STDs do not specify an age range or an interval at which screening should be repeated. Rather, they suggest that screening should be contingent on new or persistent risk factors or that, in the cases of HIV¹⁰ and hepatitis C,⁹ repeated screening is not necessary for most individuals. We eliminate this ambiguity for several STDs by imposing the assumption that females and men who have sex with men receive one test per sexual partner, of which we assume there are four⁷⁴ for females and six⁷⁵ for MSM in a lifetime, on average. This assumption is not relevant for the non-MSM male subpopulations because these individuals are not presumed to be at increased risk for any of the STDs considered.

Another complication arising from the STD screening guidelines is that the USPSTF and CDC⁷⁶ recommend additional tests during each pregnancy for most STDs, usually at the first prenatal visit (although high-risk pregnant women may benefit from repeated screening closer to delivery). The exceptions to this are chlamydia and gonorrhea, for which the USPSTF finds no evidence of substantial net benefits from screening average-risk pregnant women⁴ and the CDC only advocates additional tests for average-risk pregnant women under 25,⁷⁶ which is younger than the mean age of pregnancy in the United States.⁷⁷ As such, we assume one

additional screening occasion per pregnancy for hepatitis B, hepatitis C, HIV, and syphilis and no additional screening occasions per pregnancy for chlamydia and gonorrhea.

Finally, we employ our conservative approach when determining the number of screening occasions recommended in a lifetime for lung cancer and prostate cancer. For lung cancer, the USPSTF recommends annual screening with low-dose computed tomography for individuals between the ages of 50 and 80 who have a 20 pack-year history and who either currently smoke or have quit within the past 15 years;¹¹ this implies 31 screening occasions in a lifetime for eligible individuals. However, since the estimated false positive rate of each low-dose CT scan is more than 20% (see Table 1 in the manuscript), a healthy individual is almost certain to receive at least one false positive from 31 low-dose CT scans. In turn, the probability that a smoker will receive at least one false positive from any screening procedure in a lifetime also approaches 100%. Because of this, and because lung cancer screening is recognized as a service with low uptake,¹¹ we instead assume that male and female smokers receive only one low-dose CT scan in a lifetime. For prostate cancer, the USPSTF endorses optional screening for males between the ages of 55 and 69, but notes that there is limited evidence regarding the optimal screening interval for this service.¹² We assume that males who elect to get screened for prostate cancer do so every two years, as recommended by the American Cancer Society⁷⁸ and the American Urological Association.⁷⁹

Section S2: Derivation of P_{id}

Suppose a healthy individual in subpopulation i gets screened the recommended number of times T_{id} for disease d in their lifetime. We aim to derive the probability P_{id} that this individual will receive at least one false positive for disease d in their lifetime.

For all $j \in \{1, 2, ..., T_{id}\}$, let A_j denote the event where the individual receives a false positive the jth time they get screened for disease d. Note that P_{id} can be thought of as the probability that at least one of $A_1, A_2, ..., A_{T_{id}}$ occurs. Therefore:

$$P_{id} = P(A_1 \cup A_2 \cup ... \cup A_{T_{id}}) = 1 - (P(A_1 \cup A_2 \cup ... \cup A_{T_{id}}))^c$$

By De Morgan's law, we have:

... =
$$1 - P(A_1^c \cap A_2^c \cap ... \cap A_{T_{id}}^c)$$

By our assumption that the results of the T_{id} screening occasions are independent (see Section 2.4 of the manuscript), we have:

... = 1 -
$$P(A_1^c) \cdot P(A_2^c) \cdot ... \cdot P(A_{T_{id}}^c) = 1 - (1 - P(A_1)) \cdot (1 - P(A_2)) \cdot ... \cdot (1 - P(A_{T_{id}}))$$

Recall from Section 2.3 that p_d denotes the probability that a healthy individual will receive a false positive for disease d from one screening occasion. It follows that for all $j \in \{1, 2, ..., T_{id}\}$, $P(A_j) = p_d$. Therefore:

... = 1 -
$$(1 - p_d) \cdot (1 - p_d) \cdot ... \cdot (1 - p_d) = 1 - (1 - p_d)^{T_{id}}$$

Thus, we arrive at equation (2) from Section 2.4:

$$P_{id} = 1 - (1 - p_d)^{T_{id}}$$

Section S3: Derivation of p_i

Recall from Section 2.4 of the manuscript that \mathcal{D}_i denotes the set of diseases for which an individual in subpopulation i is recommended to get screened at least once. Let $|\mathcal{D}_i|$ denote the size of the set \mathcal{D}_i . Suppose a healthy individual in subpopulation i gets screened the recommended number of times in their lifetime for all diseases in \mathcal{D}_i . We seek to derive the probability p_i that this individual will receive at least one false positive for at least one of the diseases in \mathcal{D}_i in their lifetime.

For all $k \in \{1, 2, ..., |\mathcal{D}_i|\}$, let B_k denote the event where the individual receives at least one false positive in a lifetime for the kth disease in \mathcal{D}_i . Note that p_i can be thought of as the probability that at least one of $B_1, B_2, ..., B_{|\mathcal{D}_i|}$ occurs. Therefore:

$$p_i = P(B_1 \cup B_2 \cup ... \cup B_{|\mathcal{D}_i|}) = 1 - (P(B_1 \cup B_2 \cup ... \cup B_{|\mathcal{D}_i|}))^c$$

By De Morgan's law, we have:

... =
$$1 - P(B_1^c \cap B_2^c \cap ... \cap B_{|\mathcal{D}_i|}^c)$$

Recall our assumption from Section 2.4 that the event of receiving at least one false positive in a lifetime for each disease in \mathcal{D}_i is independent from the same event for each of the other diseases in \mathcal{D}_i . Therefore:

... = 1 -
$$P(B_1^c) \cdot P(B_2^c) \cdot ... \cdot P(B_{|\mathcal{D}_i|}^c) = 1 - (1 - P(B_1)) \cdot (1 - P(B_2)) \cdot ... \cdot (1 - P(B_{|\mathcal{D}_i|}))$$

Recall also that P_{id} denotes the probability that a healthy individual in subpopulation i will receive at least one false positive in a lifetime for some disease $d \in \mathcal{D}_i$. Let $d_1, d_2, ..., d_{|\mathcal{D}_i|}$ denote the diseases in \mathcal{D}_i . It follows that for all $k \in \{1, 2, ..., |\mathcal{D}_i|\}$, $P(B_k) = P_{id_k}$. Therefore:

... = 1 -
$$(1 - P_{id_1}) \cdot (1 - P_{id_2}) \cdot ... \cdot (1 - P_{id_{|\mathcal{D}_i|}}) = 1 - \prod_{d \in \mathcal{D}_i} (1 - P_{id})$$

Thus, we arrive at equation (3) from Section 2.4. We can plug in $P_{id} = 1 - (1 - p_d)^{T_{id}}$ to obtain the full expression presented in Section 2.4:

$$p_i = 1 - \prod_{d \in \mathcal{D}_i} (1 - P_{id}) = 1 - \prod_{d \in \mathcal{D}_i} (1 - p_d)^{T_{id}}$$

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