Estimating the lifetime risk of a false positive screening test result

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Background

Screening outcomes and consequences

	Has disease	Does not have disease
Positive result	**True positive (TP)**	**False positive (FP)**
Negative result	**False negative (FN)**	**True negative (TN)**

- Potential consequences of false positives:
  1. Stress and anxiety[1-5]
  2. Lower compliance with future screenings[6-7]
  3. Unnecessary follow-up procedures[8]

Scope of false positive risk

- For an uninfected individual, what is the probability of receiving. . .
  - a false positive on **one screening occasion** for a **particular** disease?
  - at least one false positive in a **lifetime** for a **particular** disease?
  - at least one false positive in a **lifetime** for **any** disease?

Existing literature

- For an uninfected individual, what is the probability of receiving. . .
  - a false positive on **one screening occasion** for a **particular** disease?

Disease	Screening procedure	Estimate (SE)
Breast cancer	Mammogram	4.9% (0.1%)
Cervical cancer	Pap test	5.0% (0.1%)
Colorectal cancer	Colonoscopy	11.3% (1.3%)
Lung cancer	Low-dose CT scan	20.7% (0.1%)
Prostate cancer	PSA test	10.2% (0.3%)
Chlamydia	NAAT	0.5% (<0.1%)
Gonorrhea	NAAT	0.2% (<0.1%)
Hepatitis B	HBsAg test	2.0% (0.1%)
Hepatitis C	Anti-HCV antibody test	1.0% (0.2%)
HIV	Antigen/antibody test	0.2% (<0.1%)
Syphilis	RPR test	0.3% (<0.1%)

Existing literature

- For an uninfected individual, what is the probability of receiving. . .
  - at least one false positive in a **lifetime** for a **particular** disease?
    - Estimates range from 49% to 61% for 10 mammograms[9-10]
    - 33% for 2 low-dose CT scans[11]
  - at least one false positive in a **lifetime** for **any** disease?
    - 60% for men and 49% for women after 14 screening occasions for prostate, lung, colorectal, and ovarian cancer[12-13]
    - More comprehensive estimates: ???

Guiding questions

1. **How do we estimate the probability that an individual will receive at least one false positive result when they get screened repeatedly for multiple diseases throughout their lifetime?**

2. What *is* this lifetime probability for individuals who follow the recommended screening guidelines of the U.S. Preventive Services Task Force (USPSTF)?

3. To what extent does this lifetime probability vary according to individuals' demographic and behavioral characteristics?

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Methodology

Diseases and screening procedures

- Inclusion criteria:
  1. Cancer[14] or STD[15]
  2. USPSTF grade of C or higher[16]

Disease	Screening procedure
Breast cancer	Mammogram
Cervical cancer	Pap test
Colorectal cancer	Colonoscopy
Lung cancer	Low-dose CT scan
Prostate cancer	PSA test
Chlamydia	NAAT
Gonorrhea	NAAT
Hepatitis B	HBsAg test
Hepatitis C	Anti-HCV antibody test
HIV	Antigen/antibody test
Syphilis	RPR test

Data

The False Positives Calculator

Search

Disease	Screening test	Study ID	TP	FN	TN	FP	N	Sensitivity	Specificity	PPV	NPV
Breast cancer	Mammography	Canadian	226	76	41575	2841	44718	74.8%	93.6%	7.4%	99.8%
Breast cancer	Mammography	Malmo	118	10	15088	418	15634	92.2%	97.3%	22.0%	99.9%
Breast cancer	Mammography	Stockholm	128	21	30900	1525	32574	85.9%	95.3%	7.7%	99.9%
Breast cancer	Mammography	Swedish two-county	413	20	65311	3026	68770	95.4%	95.6%	12.0%	100.0%
Cervical cancer	Pap	ARTISTIC round 1	133	0	5338	653	6124	100.0%	89.1%	16.9%	100.0%
Cervical cancer	Pap	ARTISTIC round 2	34	1	3656	176	3867	97.1%	95.4%	16.2%	100.0%
Cervical cancer	Pap	FINNISH	267	52	61241	4239	65799	83.7%	93.5%	5.9%	99.9%
Cervical cancer	Pap	NTCC phase I	84	0	21201	771	22056	100.0%	96.5%	9.8%	100.0%
Cervical cancer	Pap	NTCC phase II	55	0	23268	770	24093	100.0%	96.8%	6.7%	100.0%
Cervical cancer	Pap	POBASCAM round 1	193	22	19400	513	20128	89.8%	97.4%	27.3%	99.9%
Cervical cancer	Pap	POBASCAM round 2	162	22	8838	612	9634	88.0%	93.5%	20.9%	99.8%
Cervical cancer	Pap	SWEDESCREEN	78	41	6120	72	6311	65.5%	98.8%	52.0%	99.3%
Chlamydia	NAAT (chlamydia)	Schacter 2003	106	13	1262	10	1391	89.1%	99.2%	91.4%	99.0%
Chlamydia	NAAT (chlamydia)	Taylor 2011	52	4	389	4	449	92.9%	99.0%	92.9%	99.0%
Chlamydia	NAAT (chlamydia)	Van Der Pol 2012a	101	3	2173	12	2289	97.1%	99.5%	89.4%	99.9%
Chlamydia	NAAT (chlamydia)	Schoeman 2012	163	20	2050	0	2233	89.1%	100.0%	100.0%	99.0%
Chlamydia	NAAT (chlamydia)	Van Der Pol 2012a	94	11	2163	1	2269	89.5%	100.0%	98.9%	99.5%
Chlamydia	NAAT (chlamydia)	Schacter 2003	68	7	503	3	581	90.7%	99.4%	95.8%	98.6%
Chlamydia	NAAT (chlamydia)	Shrier 2004	14	13	99	0	126	51.9%	100.0%	100.0%	88.4%
Chlamydia	NAAT (chlamydia)	Van Der Pol 2012a	102	4	2155	7	2268	96.2%	99.7%	93.6%	99.8%

Subpopulations and screening intervals

- 6 female subpopulations
  - Anticipated number of pregnancies *(0/1/2)*
  - History of smoking *(yes/no)*
- 8 male subpopulations
  - Has sex with men *(yes/no)*
  - History of smoking *(yes/no)*
  - Intend to get screened for prostate cancer *(yes/no)*

- Lifetime number of screening occasions based on USPSTF guidelines
  - e.g., Colonoscopy every 10 years between ages 45 and 75
    $\Longrightarrow$ 4 lifetime screening occasions

Model

Step 1 of 3

- Goal:
  - Model the probability that an individual will receive a false positive on **one screening occasion** for a **particular** disease d
- Assumptions:
  - Individual is not infected with disease d on each screening occasion

$$\widehat{p}_d = \frac{\#\text{ of FP in all studies for disease } d}{\#\text{ of FP and TN in all studies for disease } d}$$

Model

Step 2 of 3

- Goal:
  - Model the probability that an individual in subpopulation i will receive at least one false positive in a **lifetime** for a **particular** disease d
- Assumptions:
  - Individual gets screened the recommended number of times T_{id} with the primary screening procedure for disease d
  - Results for one screening occasion are independent from results for other screening occasions

$$\widehat{P}_{id} = 1 - (1 - \widehat{p}_d)^{T_{id}}$$

Model

Step 3 of 3

- Goal:
  - Model the probability that an individual in subpopulation i will receive at least one false positive in a **lifetime** for **any** disease in some set $\mathcal{D}_i$
- Assumptions:
  - Screening results for one disease are independent from screening results for other diseases

$$\widehat{p}_i = 1 - \prod_{d \in \mathcal{D}_i} (1 - \widehat{P}_{id}) = 1 - \prod_{d \in \mathcal{D}_i} (1 - \widehat{p}_d)^{T_{id}}$$

Accounting for uncertainty

- Assume that each study s can be modeled by a **multinomial random variable** $Z_s \sim \text{Multinomial}(N_s, \widehat{p}_{FP,s}, \widehat{p}_{TN,s}, \widehat{p}_{+,s})$, where:
  - N_s = sample size of study s
  - $\widehat{p}_{FP,s}$; $\widehat{p}_{TN,s}$; $\widehat{p}_{+,s}$ = proportion of observations in study s that correspond to each screening outcome (FP; TN; TP or FN)

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- Employ the **parametric bootstrap**
  - Draw from multinomial distribution to simulate results of each study
  - Use simulated data to compute one realization of $\widehat{p}_i$
  - Repeat 9,999 times to obtain $B = 10,000$ realizations of $\widehat{p}_i$

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- Compute the **standard error** of $\widehat{p}_i$, given by

$$\text{SE}(\widehat{p}_i) = \sqrt{\frac{1}{B-1}\sum_{b=1}^{B}(\widehat{p}_i^{(b)} - \bar{\widehat{p}}_i)^2}, \quad \text{where } \bar{\widehat{p}}_i = \frac{1}{B}\sum_{b=1}^{B}\widehat{p}_i^{(b)}$$

Results

Female subpopulations

Estimated lifetime false positive probability by subpopulation

Subpopulation	Estimate (SE)
Baseline females	**85.5% (0.9%)**
Females, one pregnancy	**86.0% (0.8%)**
Females, two pregnancies	**86.5% (0.8%)**
Female smokers	**88.5% (0.7%)**
Female smokers, one pregnancy	**88.9% (0.7%)**
Female smokers, two pregnancies	**89.3% (0.6%)**
Baseline males	38.9% (3.6%)
Men who have sex with men (MSM)	43.1% (3.4%)
Male smokers	51.5% (2.9%)
MSM smokers	54.9% (2.7%)
Males, routine prostate exams	74.2% (1.7%)
MSM, routine prostate exams	76.0% (1.6%)
Male smokers, routine prostate exams	79.6% (1.3%)
MSM smokers, routine prostate exams	81.0% (1.2%)

Male subpopulations

Estimated lifetime false positive probability by subpopulation

Subpopulation	Estimate (SE)
Baseline females	85.5% (0.9%)
Females, one pregnancy	86.0% (0.8%)
Females, two pregnancies	86.5% (0.8%)
Female smokers	88.5% (0.7%)
Female smokers, one pregnancy	88.9% (0.7%)
Female smokers, two pregnancies	89.3% (0.6%)
Baseline males	**38.9% (3.6%)**
Men who have sex with men (MSM)	**43.1% (3.4%)**
Male smokers	**51.5% (2.9%)**
MSM smokers	**54.9% (2.7%)**
Males, routine prostate exams	**74.2% (1.7%)**
MSM, routine prostate exams	**76.0% (1.6%)**
Male smokers, routine prostate exams	**79.6% (1.3%)**
MSM smokers, routine prostate exams	**81.0% (1.2%)**

Discussion

Answers to guiding questions

1. How do we estimate the probability that an individual will receive at least one false positive result when they get screened repeatedly for multiple diseases throughout their lifetime?
   -
2. What *is* this lifetime probability for individuals who follow the recommended screening guidelines of the U.S. Preventive Services Task Force (USPSTF)?
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3. To what extent does this lifetime probability vary according to individuals' demographic and behavioral characteristics?
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Answers to guiding questions

1. How do we estimate the probability that an individual will receive at least one false positive result when they get screened repeatedly for multiple diseases throughout their lifetime?
   - $$\widehat{p}_i = 1 - \prod_{d \in \mathcal{D}_i} (1 - \widehat{P}_{id}) = 1 - \prod_{d \in \mathcal{D}_i} (1 - \widehat{p}_d)^{T_{id}}$$
2. What *is* this lifetime probability for individuals who follow the recommended screening guidelines of the U.S. Preventive Services Task Force (USPSTF)?
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   - **At least 85% for females, 38% for males**
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2. What *is* this lifetime probability for individuals who follow the recommended screening guidelines of the U.S. Preventive Services Task Force (USPSTF)?
   - **At least 85% for females, 38% for males**
3. To what extent does this lifetime probability vary according to individuals' demographic and behavioral characteristics?
   - **Substantial variation among males (38%-81%)**
   - **Little variation among females (85%-89%)**

Limitations

1. **Estimated probabilities are only valid for uninfected individuals**
2. Assumption of perfect adherence to USPSTF screening guidelines may not hold in practice[17-19]
3. Considered only the primary screening procedure for each disease
4. Difficult to determine lifetime number of STD screening occasions since STD guidelines are highly individualized

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Summarizing our contribution

What:

- Novel framework for quantifying the lifetime risk of a false positive
  - Incorporates multiple diseases and demographic characteristics
  - Easy to update as more data become available

Why:

- Improve patients' perspective on screening technology
- Facilitate transparent communication by healthcare providers

How:

- Manuscript available on arXiv
- R Shiny dashboard

References & Links

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Links

https://linktr.ee/timwhite_jsm2022