Evaluation of Population-Based Organized Service Screening (POSS): From Universal to Precision Screening Strategies

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Evolution from Universal to Precision Screening

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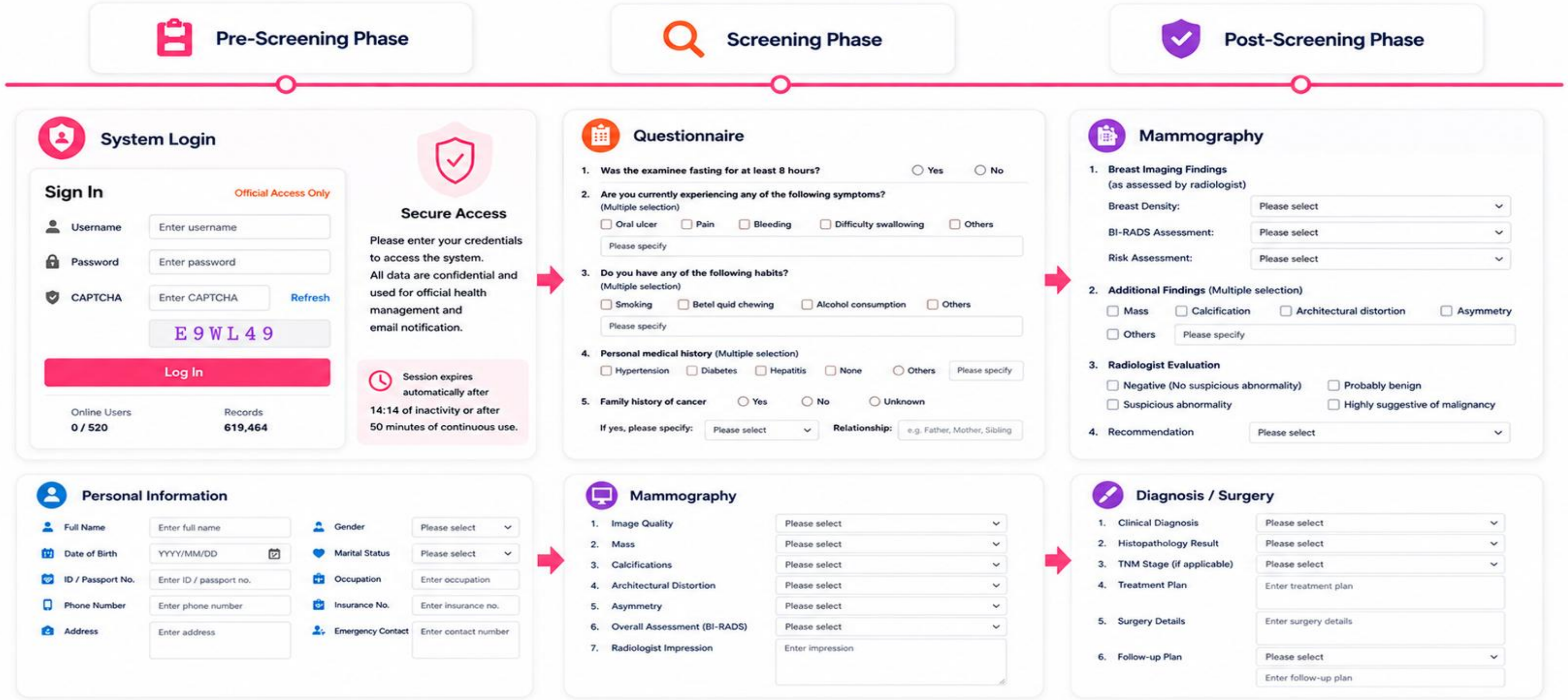
Population-based Organized Service Screening Process

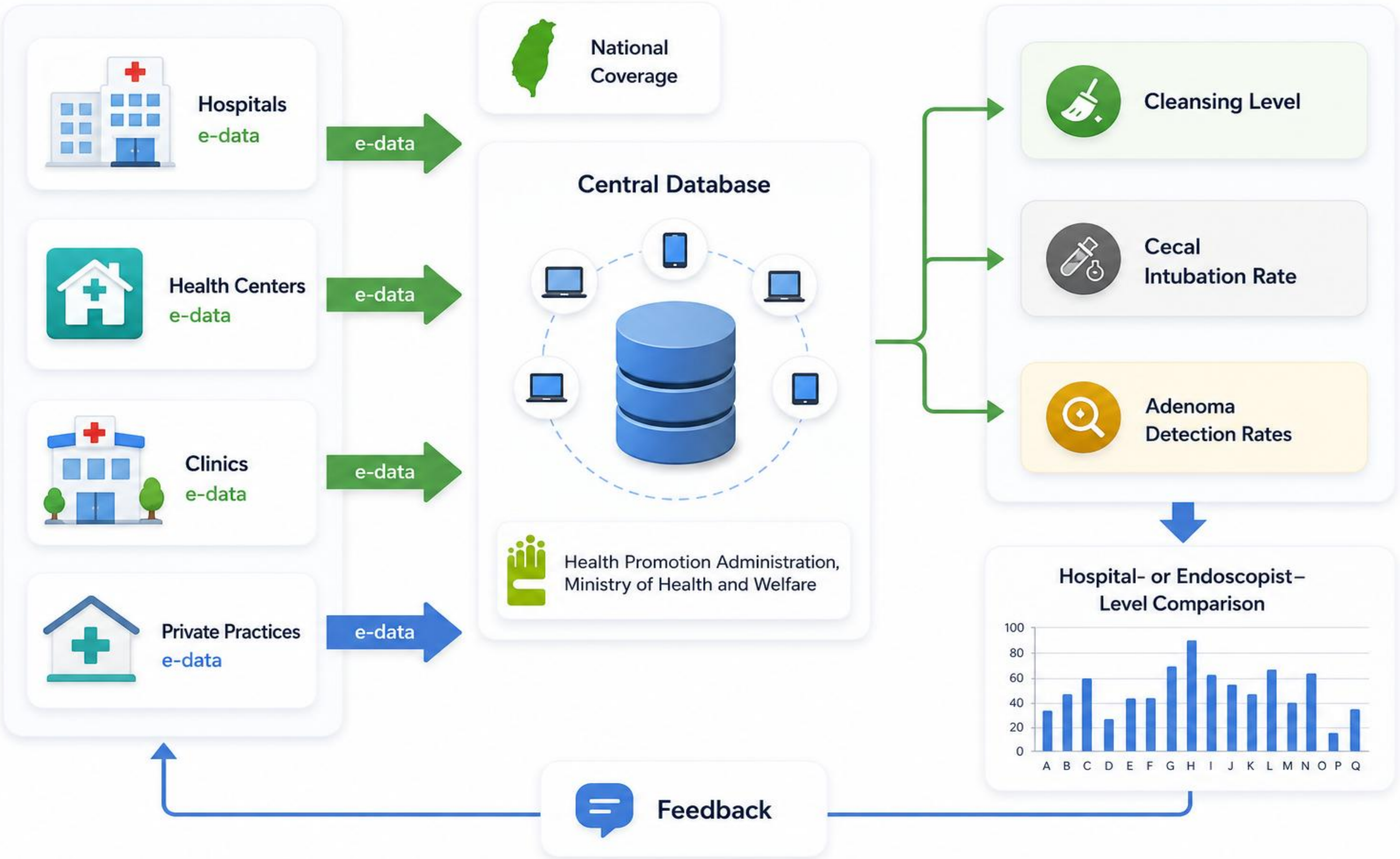
1. **Eligible Population**
   - **Invitation list**
   - Population and Screening Registration Systems
2. **Invitation**
   - **Call-recall invitation**
   - by letters, phone calls, and in-person invitations
3. **Screening**
   - **Out-reach/In-reach**
   - Community/Health Center/Clinics/ Hospitals
4. **Report Delivery**
   - **Assessment & consultation**
5. **Referral**
   - **Follow-up & health management**

Quality Index

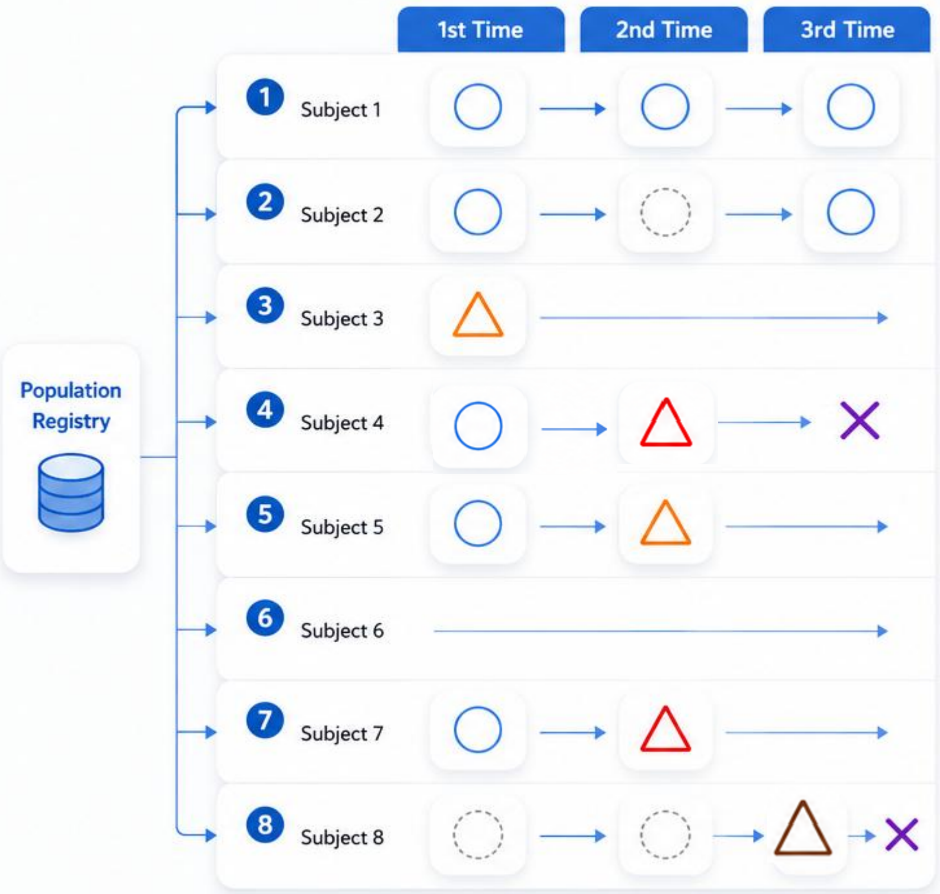
- Participation Rate
- Positive Rate
- Referral Rate
- Cancer Detection Rate

Web-Based Registry System for Nationwide Screening Programme on Breast Cancer, Oral Cancer, and Colorectal Cancer

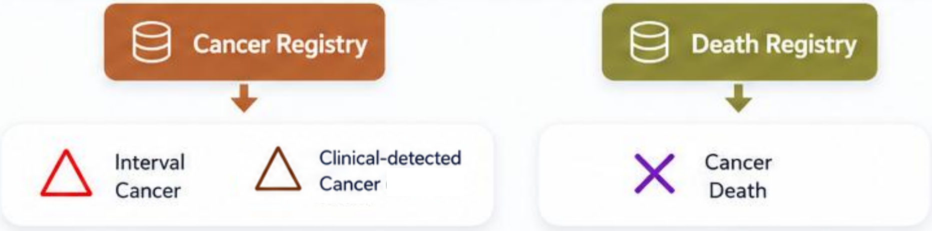



Hospitals
e-data
Health Centers
e-data
Clinics
e-data
Private Practices
e-data
e-data
e-data
e-data
e-data
National Coverage
Central Database
Health Promotion Administration, Ministry of Health and Welfare
Cleansing Level
Cecal Intubation Rate
Adenoma Detection Rates
Hospital- or Endoscopist-Level Comparison
100
80
60
40
20
0
A B C D E F G H I J K L M N O P Q
Feedback

Dynamic Screening Data Collection in Population-based Organized Service Screening



Subject	Screening Date	Screening Result	Cancer Detection Mode	Diagnosis Date	Death Date
1	2026	Negative	Normal	-	-
1	2028	Negative	Normal	-	-
1	2030	Negative	Normal	-	-
2	2026	Negative	Normal	-	-
2	2030	Negative	Normal	-	-
3	2026	Positive	SDC	2026	-
4	2027	Negative	Normal	-	-
4	2028	Negative	IC	2028	2036
…	…	…	…	…	…
8	-	-	CDC	2036	2040



Changhua Community-Based Integrated Screening: A Platform for Delivering Preventive Services

H. pylori eradication

Behaviour change counseling

Nutrition education

Exercise instruction

- **Screening for 7 neoplastic diseases**
  - National policy: breast, oral, cervical, colorectal cancer, lung cancer; Liver cancer and liver-related diseases; gastric cancer
- **9 non-neoplastic chronic diseases**
  - Diabetes, hypertension, hyperlipidemia, TB, depression disorder, CKD, COPD, osteoporosis, frailty
- **Surveillance of behavioral risk factors**
  - Smoking, betel nut chewing, BMI; physical fitness testing (2019-)

Dx & Tx of malignancies

HCV elimination

Psychological Counseling

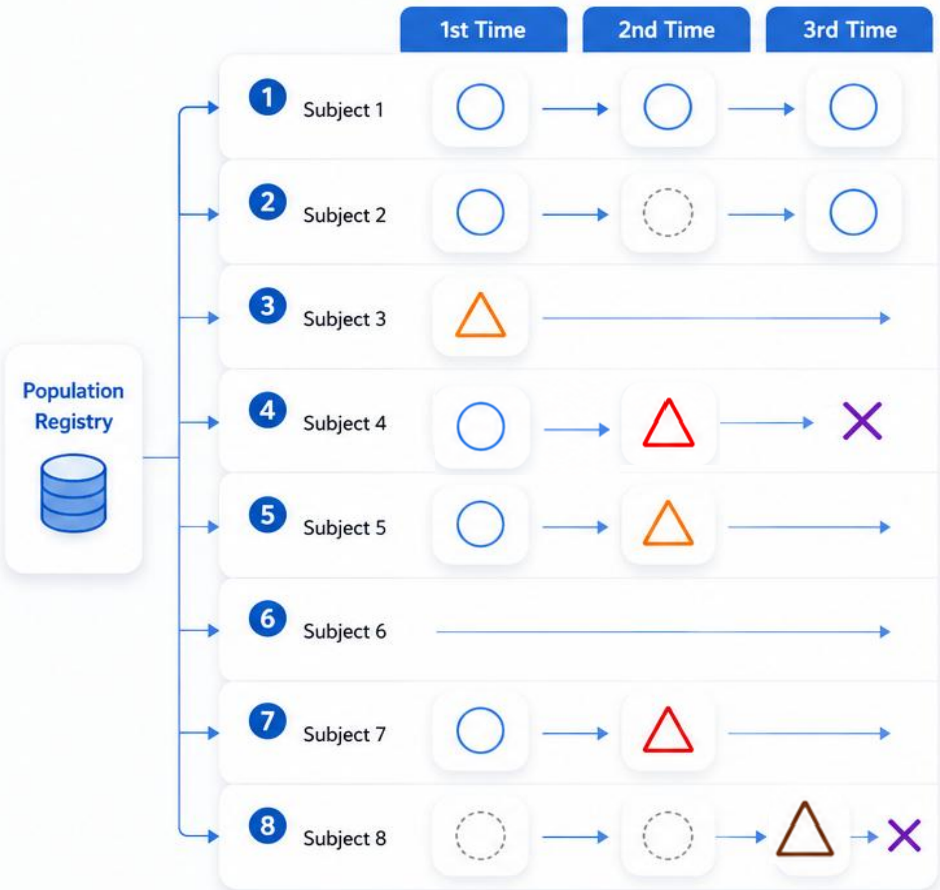
DOTS

Information Systems of Community-based Screening

Community-based Integrated Screening Data

Items	Source	Character	Renewal
Population registry	Bureau of Census	Secondary data	Annually
Pap smear screening registry	Ministry of Health	Secondary data	Annually
Cancer registry	Ministry of Health	Secondary data	Annually
National health insurance	Bureau of National Health Insurance	Claim data	Annually
Mortality registry	Ministry of Health	Secondary data	Annual update from national mortality and weekly update from local mortality data
Questionnaire	Community-based Risk Factor Survey	Primary data	Annually
Biochemical data	Community-based Screening	Primary data	Depends on disease
Follow-up system	Referral Hospital	Primary data	Depends on disease

Dynamic Screening Data Collection in Population-based Organized Service Screening



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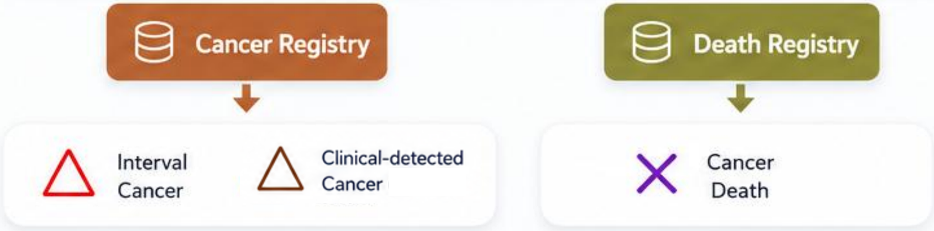
2	2030	Negative	Normal	-	-
3	2026	Positive	SDC	2026	-
4	2027	Negative	Normal	-	-
4	2028	Negative	IC	2028	2036
…	…	…	…	…	…
8	-	-	CDC	2036	2040

Community Data

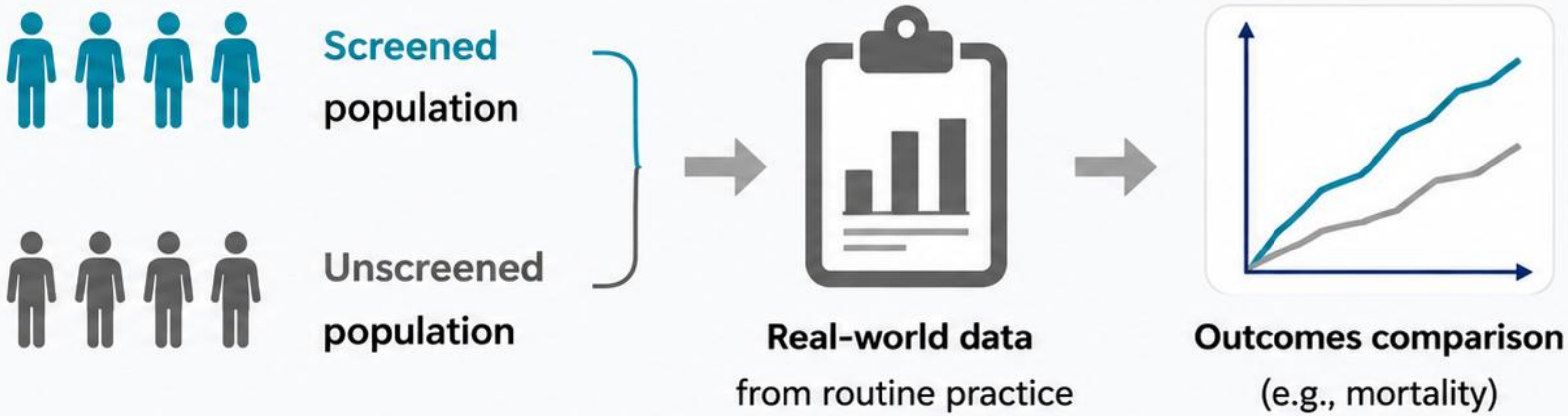
Mets	Exercise	…
Y	N	…
Y	N	…
N	N	…
N	Y	…
N	Y	…
Y	N	…
Y	N	…
Y	N	…



But What Happens After Implementation?

Once screening programs are implemented nationwide, we rely on observational data from routine practice.

Observational Comparisons in Practice



Key Question

How can we evaluate screening effectiveness in the real world when a randomized control group no longer exists?

Limitations: Traditional Approaches Are Subject to Major Biases

Lead-time Bias
Earlier diagnosis looks better, even if time of death is unchanged.

Length Bias
Slow-growing tumors are more likely to be detected by screening.

Self-selection Bias
People who participate in screening are healthier and have different risk profiles.

Bias from Three Dimensions in Evaluation of Screening Program

Patient

Self-selection bias

- Health awareness
- Health-seeking behavior
- Different risk profiles
- Socioeconomic factors

Disease

Lead-time bias & Length bias

- Earlier diagnosis without changing outcome
- Slow-growing disease more likely detected

Program Evaluator & Health Policy-maker

Provider

Measurement Error, Self-selection bias, Delay treatment or therapy

- Diagnostic variability
- Different management strategies
- Delay in treatment or referral

Bias Adjustment

Intention-to-treat

$$RR = \frac{P(D \mid I)}{P(D \mid \bar{I})} = \frac{P(D \mid S)P(S \mid I) + P(D \mid \bar{S})P(\bar{S} \mid I)}{P(D \mid \bar{I})}$$

D: indicates death from cancer,
I: invitation to screening
S: actually receiving screening.

$$RR_1 = \frac{P(D \mid S)}{P(D \mid \bar{I})} \qquad RR_2 = \frac{P(D \mid \bar{S})}{P(D \mid \bar{I})}$$

$$RR = \frac{P(D \mid S)}{P(D \mid \bar{I})}\, p + \frac{P(D \mid \bar{S})}{P(D \mid \bar{I})}\,(1-p) = RR_1 \cdot p + RR_2(1-p)$$

Adjusted:
P: the proportion of those invited who actually attend screening

Key Takeaway

Bias from patient, disease, and provider levels can lead to substantial misestimation of screening effectiveness.

Why It Matters

Unadjusted comparisons may overestimate benefits and misguide health policy and resource allocation.

Our Goal

Use robust bias adjustment methods to obtain unbiased estimates of screening effectiveness.

Population-based Screening Policy
(Population-level approach)

1. **Universal screening tool**
   The same screening tool for everyone.
   Example: PSA
2. **Equal-spaced inter-screening interval**
   The same interval for everyone.
   Example: Every 4 years
3. **Average-risk approach**
   Applied to the general population.
   Example: Men aged 55 to 69

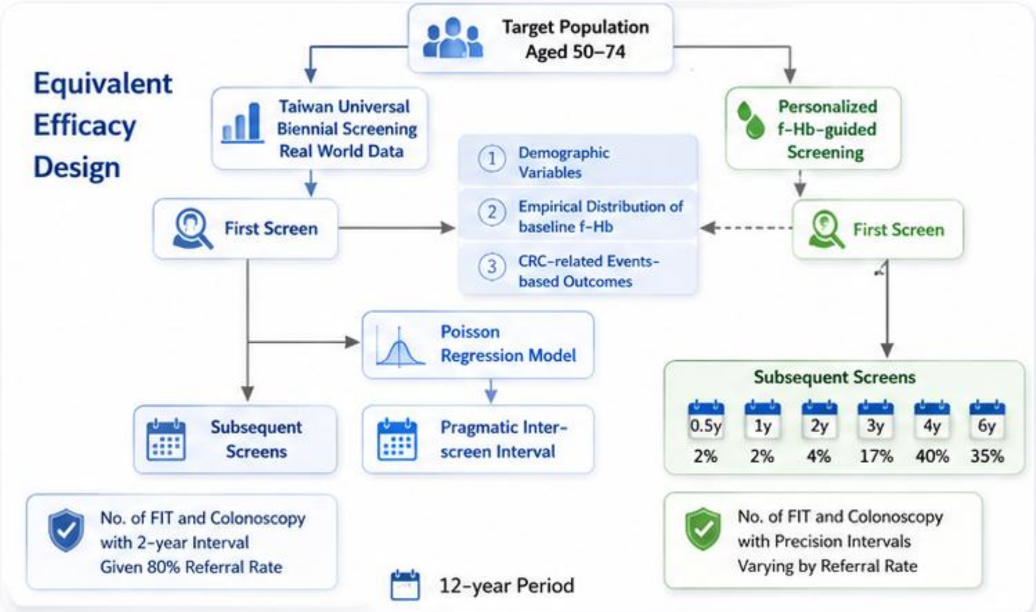
VS.

Individual-tailored Approach
(Individual-level approach)

1. **Diversified screening tools**
   Different tools used according to individual risk factors.
   Example: PSA, fPSA, PHI, 4Kscore, etc.
2. **Different inter-screening intervals**
   Intervals are tailored based on individual risk.
   Example: 1–10 years depending on risk
3. **Identify high-risk and average-risk**
   Stratify individuals by age, PSA level, family history, genetic risk, etc.
   Example: Age, PSA, family history, genetics

f-Hb-guided Precision Screening

f-Hb (µg/g)	Interval (years)
Undetectable	6
1–9	4
10–19	3
20–49	2
50–100	1
100–149	1
150+	0.5



JAMA Oncology

Precision Colorectal Cancer Fecal Immunological Test Screening With Fecal-Hemoglobin-Concentration–Guided Interscreening Intervals

Amy Ming-Fang Yen, PhD; Chen-Yang Hsu, PhD; Ting-Yu Lin, PhD; Chiu-Wen Su, PhD; Han-Mo Chiu, PhD; Tony Hsiu-Hsi Chen, PhD; Sam Li-Sheng Chen, PhD

	Universal Biennial Screening	f-Hb-guided Personalized CRC Screening		
		60% Referral Rate	80% Referral Rate	100% Referral Rate
No. of Tests	19.9 M		10.2 M	
Reduction in No. of Tests	Ref.		9.6 M	
Reduction(%) in Tests	Ref.		49%	
No. of Colonoscopies	1.28 M	686 K	915 K	1.1 M
Reduction in No. of Colonoscopies	Ref.	593 K	364 K	135 K
Reduction(%) in Colonoscopies	Ref.	46%	28%	11%

Yen AMF, et al, JAMA Oncol. 2024;doi:10.1001/jamaoncol.2024.0961.

PLCO

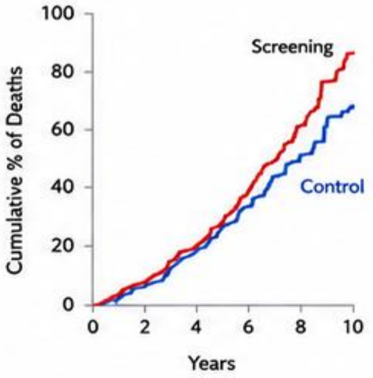
The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial

ERSPC

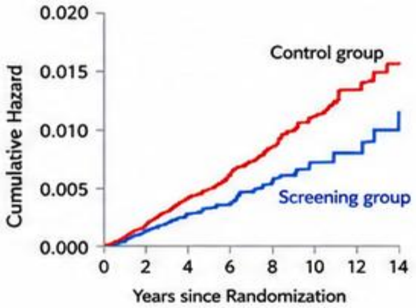
European Randomized Study of Screening for Prostate Cancer

Published in *The New England Journal of Medicine*

1 2009;360:1310-9.

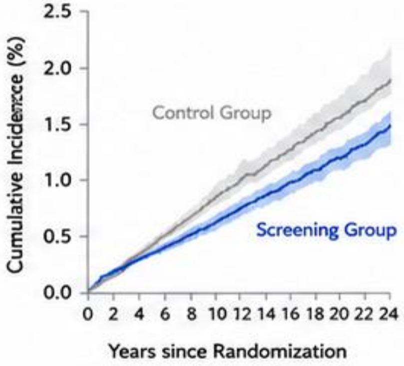


2 2009;360:1320-8.



No. at Risk	0 yr	8 yr
Screening group	65,078	34,690
Control group	60,101	31,534

3 2025; 393:1669-1680



PLCO, 7-yr follow-up
RR = 1.13
(0.75–1.70)

ERSPC, 8-yr follow-up
RR = 0.80
(0.65–0.98)

ERSPC, 23-yr follow-up
RR = 0.87
(0.80–0.95)

One-Size-Fits-All PSA-based Screening: Pros & Cons

Under Debate!

PSA-Based Screening

for the General Population

Benefits

- Reduces prostate cancer mortality
- Improves quality of life

Harms

- False positives, overdiagnosis
- False negatives, anxiety

- Large-scale population screening
- Balance benefits and harms
- Need for better risk stratification and policies

Oncology: Prostate/Testis/Penis/Urethra

THE JOURNAL of UROLOGY®

CrossMark

Risk Prediction of Prostate Cancer with Single Nucleotide Polymorphisms and Prostate Specific Antigen

Sam Li-Sheng Chen, Jean Ching-Yuan Fann, Csilla Sipeky, Teng-Kai Yang, Sherry Yueh-Hsia Chiu, Amy Ming-Fang Yen, Virpi Laitinen, Teuvo L. J. Tammela, Ulf-Håkan Stenman, Anssi Auvinen, Johanna Schleutker and Hsiu-Hsi Chen*

Posterior odds of prostate cancer by PSA based on 7 SNPs in Finnish prostate cancer screening trial

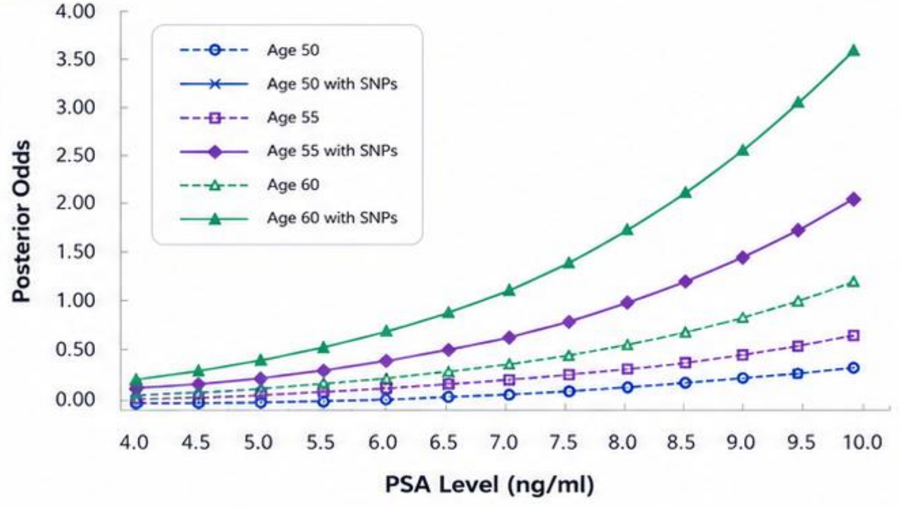
	Estimated Likelihood Ratio Given PSA	Estimated PSA + 7 SNP Posterior Odds (95% CI)	
Formula	$P(PSA\|D)/P(PSA\|\bar{D})$	$\frac{P(D)}{P(\bar{D})}$ × (likelihood ratio given PSA) × (SNP specific risk)*	
PSA at age less than 60 (ng/ml):			
4.0	3.8	3.7	(1.6 – 10)
4.5	5.5	5.4	(2.2 – 15.3)
5.0	7.7	7.6	(3 – 23.3)
5.5	10.7	10.5	(3.9 – 33.6)
6.0	14.5	14.2	(5.2 – 47.5)
6.5	19.3	18.8	(6.5 – 65.7)
7.0	25.3	25.7	(8.4 – 89.1)
7.5	32.7	31.9	(10.3 – 122.6)
8.0	41.8	40.7	(12.9 – 157.4)
8.5	52.9	51.5	(15.6 – 207)
9.0	66.1	64.9	(18.9 – 267)
9.5	81.9	79.8	(22.6 – 348.4)
10.0	100.8	98.2	(27.28 – 437.5)
PSA at age 63–71 (ng/ml):			
4.0	1.39	1.3	(0.6 – 3)
4.5	1.86	1.8	(0.8 – 4.2)
5.0	2.42	2.3	(1.1 – 5.6)
5.5	3.10	2.9	(1.3 – 7.5)
6.0	3.89	3.7	(1.6 – 10)
6.5	4.82	4.6	(2 – 12.7)
7.0	5.90	5.6	(2.4 – 16)
7.5	7.16	6.8	(2.8 – 20.1)
8.0	8.60	8.2	(3.2 – 24.7)
8.5	10.25	9.7	(3.8 – 30.2)
9.0	12.14	11.5	(4.4 – 36.7)
9.5	14.27	13.6	(5 – 44.5)
10.0	16.64	15.7	(5.7 – 54)

For 7 SNPs likelihood ratio was 1.88 (95% CI 1.42–2.49) for rs4242382, 1.68 (95% CI 1.35–2.09) for rs10486567, 1.45 (95% CI 1.18–1.77) for rs1601979, 1.54 (95% CI 1.36–1.74) for rs6983267, 8.98 (95% CI 5.51–14.65) for rs138213197, 1.93 (95% CI 1.46–2.56) for rs1447295 and 1.42 (95% CI 1.25–1.61) for rs1859962 using calculation,

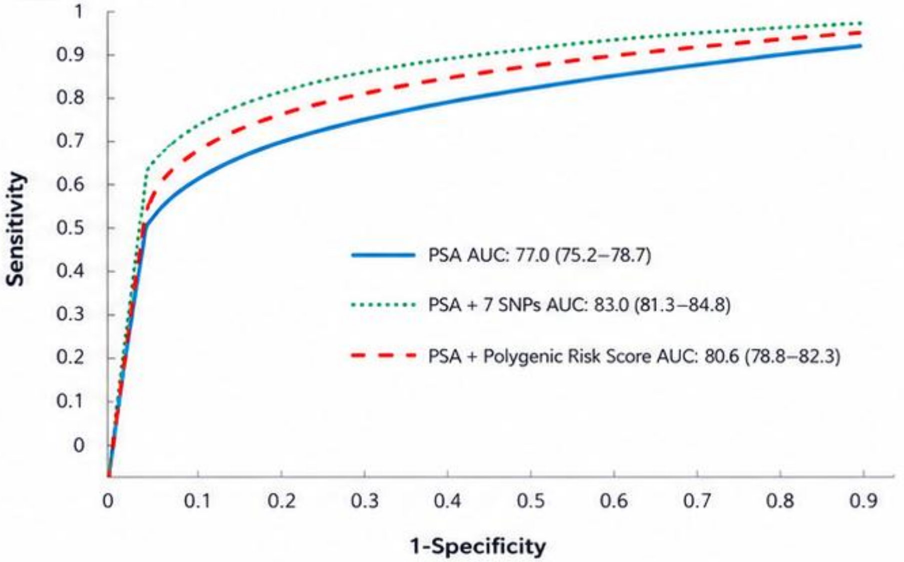
$P(SNP^1, SNP^2, ..., SNP^7|D) \times \log(1.88) + \log(1.68) + \log(1.45) + \log(1.54) + 0.0367 \times \log(1.98) + 0.0483 \times \log(8.98) + 0.0441 \times \log(1.42) = 2.8.$

* Estimated SNP specific risk calculated as $\frac{P(SNP^1, SNP^2, ..., SNP^7|D)}{P(SNP^1, SNP^2, ..., SNP^7|\bar{D})}$ was 2.8 at age less than 60 and 63 to 71 years.

Posterior Odds by PSA Level and Age Group



ROC Curves for Prostate Cancer Prediction Models



genes MDPI

Article

Gene-Prostate-Specific-Antigen-Guided Personalized Screening for Prostate Cancer

Teng-Kai Yang [1,2,3], Pi-Chun Chuang [3,4], Amy Ming-Fang Yen [5], Hsiu-Hsi Chen [2] and Sam Li-Sheng Chen [5,*]

The six-state (normal, over-detected, early and late PrCa in pre-clinical phase, and early and late PrCa in clinical phase) Markov model was developed in combination with PSA level and genetic variants for Risk Calculation.

A computer-based simulated RCT was designed to estimate the reduction of mortality and screening utilization between three arms, personalized screening, universal screening, and non-screening group.

The 10-year Risk of Developing Prostate Cancer, With the Positive and Negative Likelihood Ratios by PSA Levels and Genetic Risk Groups

Prostate-Specific Antigen (ng/mL)	Genetic Risk	10-Year Risk for Prostate Cancer	Positive Likelihood Ratio (LR+)	Negative Likelihood Ratio (LR−)
>10	High	72.5%	–	0.93
>10	Low	30.9%	69.17	0.87
8.01–10	High	43.0%	25.59	0.89
8.01–10	Low	15.0%	39.23	0.74
6.01–8	High	27.3%	10.12	0.82
6.01–8	Low	8.1%	18.06	0.50
4.01–6	High	17.4%	5.26	0.75
4.01–6	Low	4.9%	10.65	0.48
3.01–4.0	High	15.0%	4.71	0.65
3.01–4.0	Low	4.2%	7.71	0.28
2.01–3.0	High	10.7%	2.69	0.51
2.01–3.0	Low	2.9%	5.45	0.24
1.01–2.0	High	4.7%	2.40	0.31
1.01–2.0	Low	1.2%	2.83	0.08
0–1.0	High	1.3%	1.30	0.18
0–1.0	Low	0.3%	1.55	0.09

Yang, Genes, 2019

$$LR+ = \frac{\text{sensitivity}}{\text{specificity}}$$

$$LR- = \frac{1 - \text{sensitivity}}{\text{specificity}}$$

The Recommended Age to Start Screening and the Screening Interval by PSA Level and Combined Genetic Risk Among Subjects Susceptible to Progressive Prostate Cancer

Prostate-Specific Antigen, ng/mL	Genetic Risk	Screening Starting Age, Years	Screening Interval, Years
>10	High	47	1
>10	Low	50	1
8.01–10	High	47	1
8.01–10	Low	52	3
6.01–8	High	50	2
6.01–8	Low	55	4
4.01–6	High	52	3
4.01–6	Low	55	4
3.01–4.0	High	52	3
3.01–4.0	Low	55	4
2.01–3.0	High	52	3
2.01–3.0	Low	55	4
1.01–2.0	High	55	4
1.01–2.0	Low	60	12
0–1.0	High	60	12
0–1.0	Low	60	12

Simulated Results of No screening, Universal, and Gene-PSA Personalized Prostate Cancer Screening

	NSG (Non-screening group)	USG (Universal screening group)	PSG (Personalized screening group)
Participants	15,000	15,000	15,000
Prostate cancer deaths, n	384	307	299
Mortality reduction, rate ratio (95% CI)	Reference	0.80 (0.67–0.91)	0.78 (0.69–0.93)
High-grade cancers, n	251	158	148
Incidence reduction, rate ratio (95% CI)	Reference	0.63 (0.52–0.77)	0.59 (0.48–0.72)
Number of PSA tests, n	–	88,673	65,586
Test reduction, %	–	Reference	26
Over-detection cases, n	–	193	190
% of avoid over-detection	–	Reference	2

NSG: non-screening group; USG: universal screening group; PSG: personalized screening group.

Personalized screening program:

1. Reduced 22% (9%–33%) death from PrCa compared with 20% (7%–21%) noted in the universal screening group.
2. Dispensed with 26% of unnecessary PSA test.
3. Avoid unnecessary over-detection cases by 2%.

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2. Dispensed with 26% of unnecessary PSA test.
3. Avoid unnecessary over-detection cases by 2%.

Final Remarks

- Comprehensive data collection is fundamental for evaluating screening quality, effectiveness, and developing precision screening.
- Bias correction is necessary to obtain robust estimates of screening effectiveness in organized service screening programs.
- Precision screening requires validation through randomized trials and evaluation still required after implementation of service screening.

Thank you for your attention!