Whom to screen, when and how

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Mammography screening guidelines

PR China	United States (USPSTF)	United Kingdom (NHS)
Women with an average risk of breast cancer age 45-65 should undergo mammography screening every two years	Women with an average risk of breast cancer age 50-74 should undergo mammography screening every two years	All women with average risk of breast cancer are invited to mammography screening every three years form age 50 to 70.
Women aged 40-45 may receive mammography screening after discussion of risks and benefits with their doctors	Women aged 40-49 may receive mammography screening after discussion of risks and benefits with their doctors	Women aged 40-49 with moderate or high risk because of their family history should undergo screening.
Women with a first-degree family history of early-onset breast cancer should start screening at age 35	Women with a first-degree family history of early-onset breast cancer may start screening at age 40	Women who carry pathogenic variants in *BRCA1/2* should received yearly MRI screens starting at age 30.

Mammography screening guidelines

PR China		om (NHS)
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Box 1. **Wilson and Jungner classic screening criteria**[1]

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Mammography screening guidelines

PR China	United States (USPSTF)	United Kingdom (NHS)
Women with an average risk of breast ca… undergo r… screening… Women a… mammog… discussio… with their… Women w… family his… breast cancer should start screening at age 35	Women with an average risk of … breast cancer may start screening at age 40	All women with average risk of … d to …ng every …) to 70. …h …ecause …hould …ogenic …ould received yearly MRI screens starting at age 30.

While screening mammography in women aged 40 to 49 years may reduce the risk for breast cancer death, the number of deaths averted is smaller than that in older women and the number of false-positive results and unnecessary biopsies is larger. The balance of benefits and harms is likely to improve as women move from their early to late 40s.

–US Preventive Services Task Force

Sufficiently informative risk estimates could inform targeted screening strategies

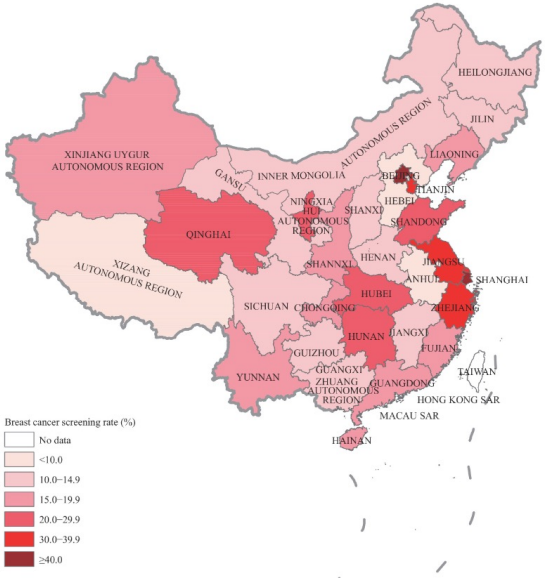
USPSTF is currently reviewing its guidelines:

*Key Question 1. What is the comparative effectiveness of different mammography-based breast cancer screening strategies (e.g., by modality, interval, initiation age, use of supplemental imaging, or **personalization based on risk factors**) on breast cancer morbidity and breast cancer–specific or all-cause mortality?*

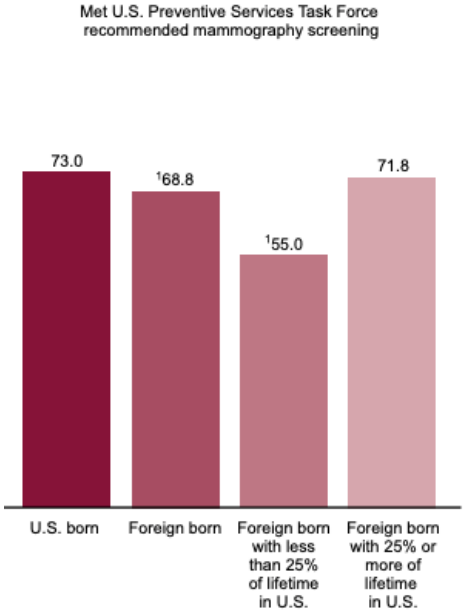
(emphasis added)

Mammography screening guidelines: coverage gaps

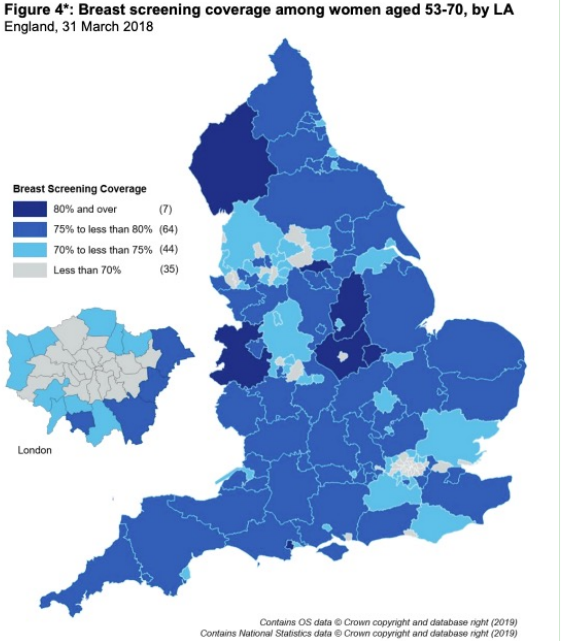
PR China



United States (USPSTF)

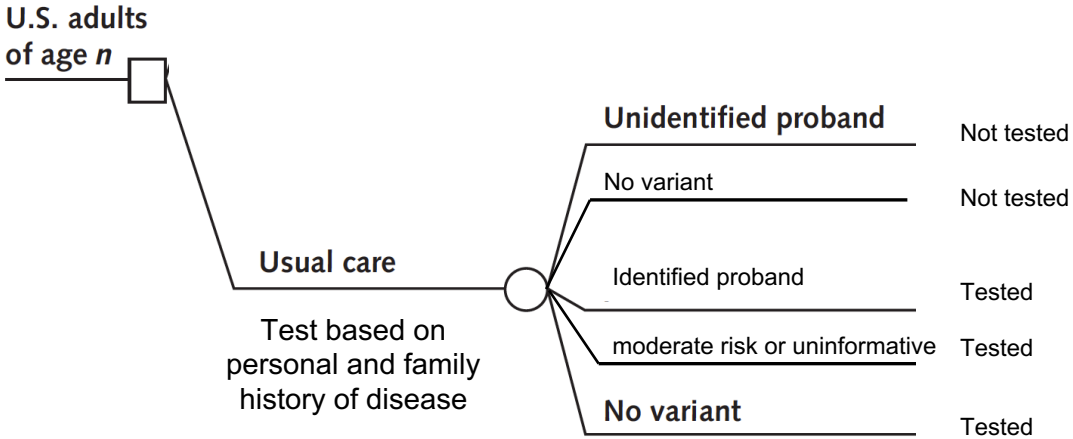


United Kingdom (NHS)



https://weekly.chinacdc.cn/en/article/doi/10.46234/ccdcw2021.078
https://www.cdc.gov/nchs/data/nhsr/nhsr129-508.pdf
https://files.digital.nhs.uk/60/77DCCC/breast-screening-programme-eng-2017-18-report.pdf

Genetic testing for HBOC, LS and FH: current clinical guidelines



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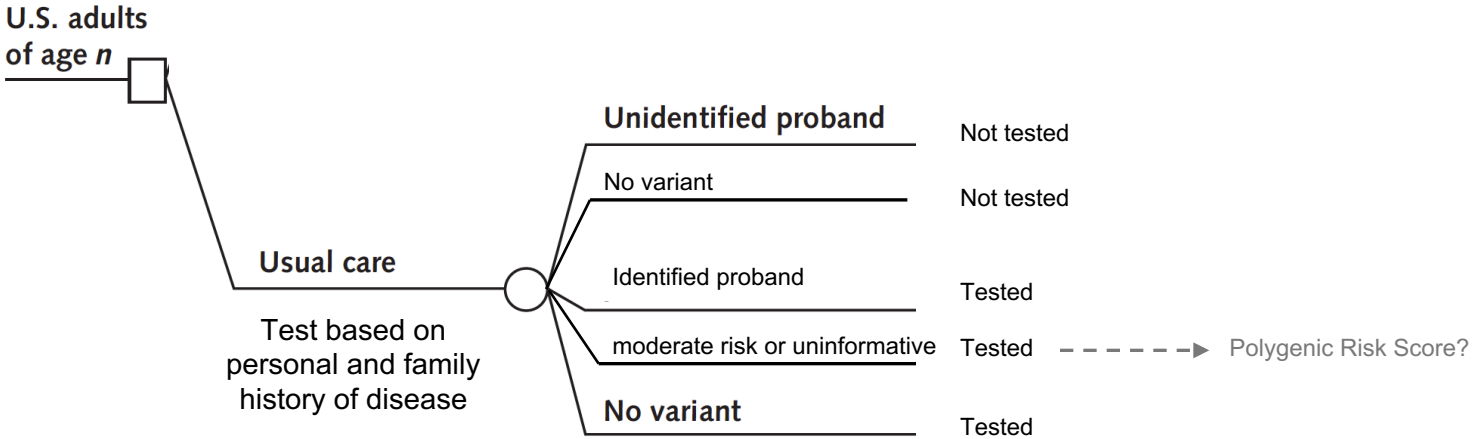
Genetic testing for HBOC, LS and FH: current clinical guidelines



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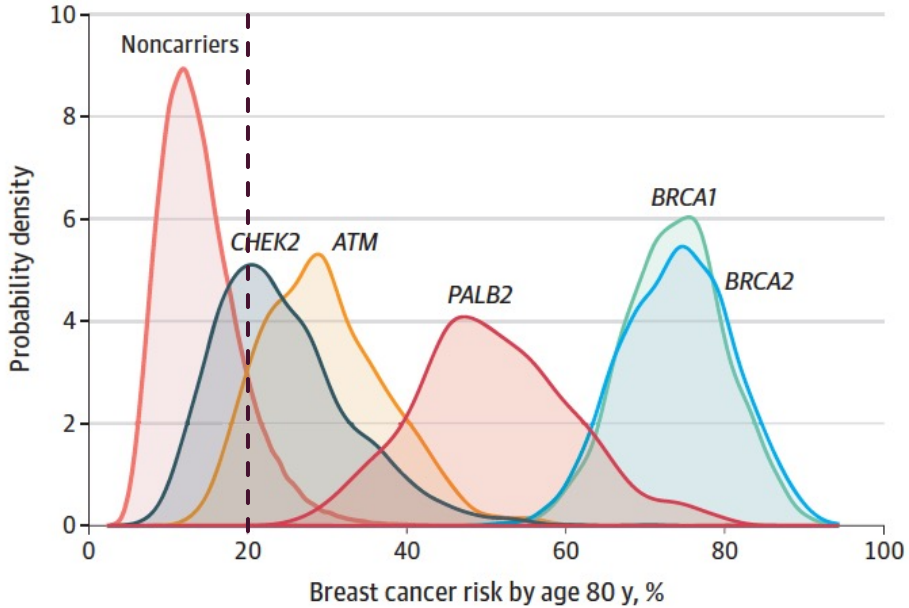
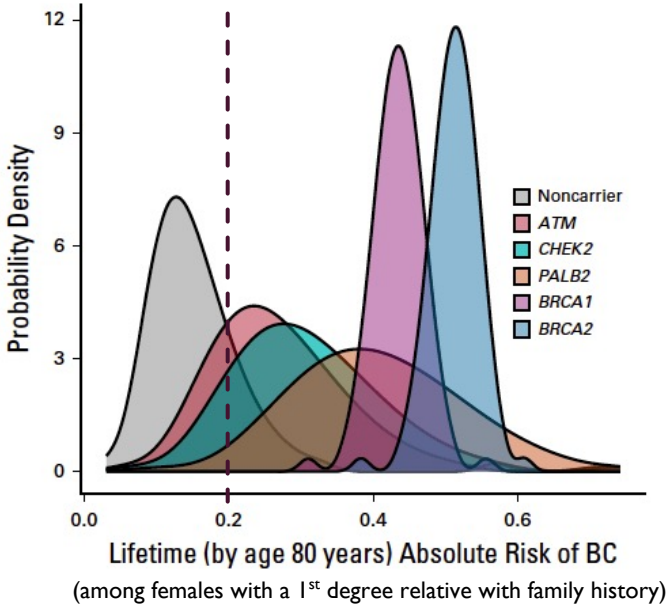
Slide Courtesy of Sarah Kalia

PRS Describes Distribution of Risk for Female Carriers of Moderate/High Penetrance Variant

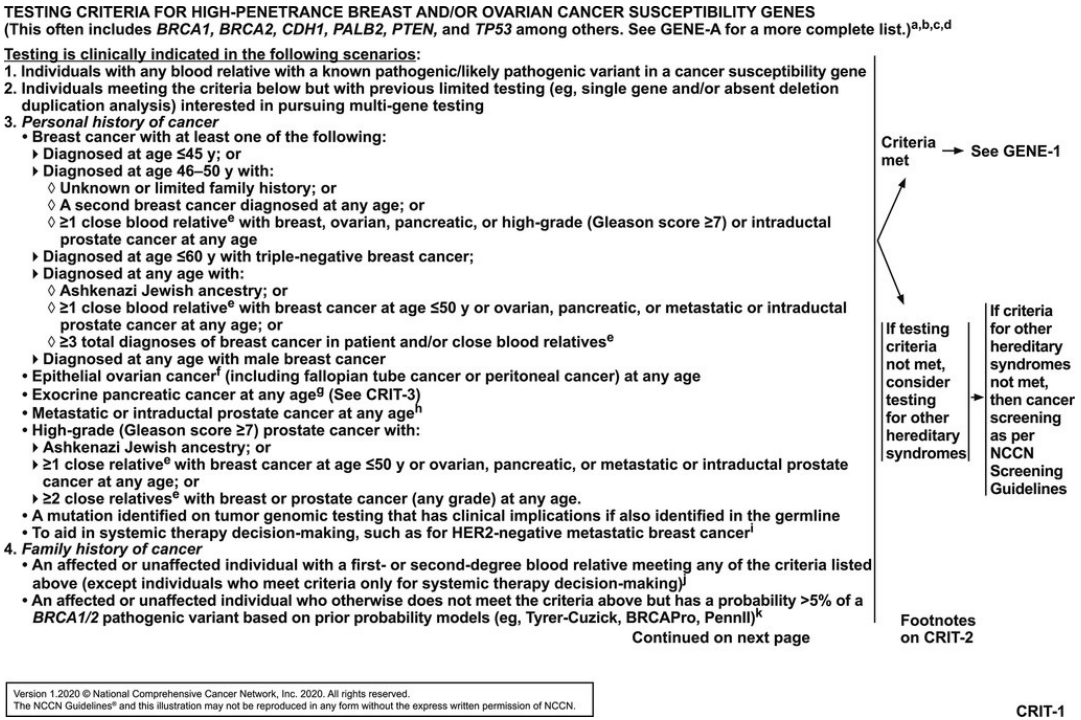




(among females with a 1st degree relative with family history)

Gallagher (2020) *JAMA Netw Open*; Gao (2021) *J Clin Oncol*

Complex guidelines are difficult to implement



TESTING CRITERIA FOR HIGH-PENETRANCE BREAST AND/OR OVARIAN CANCER SUSCEPTIBILITY GENES
(This often includes *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53* among others. See GENE-A for a more complete list.)[a,b,c,d]

Testing is clinically indicated in the following scenarios:

1. Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
2. Individuals meeting the criteria below but with previous limited testing (eg, single gene and/or absent deletion duplication analysis) interested in pursuing multi-gene testing
3. *Personal history of cancer*
   - Breast cancer with at least one of the following:
     - Diagnosed at age ≤45 y; or
     - Diagnosed at age 46–50 y with:
       - ◊ Unknown or limited family history; or
       - ◊ A second breast cancer diagnosed at any age; or
       - ◊ ≥1 close blood relative[e] with breast, ovarian, pancreatic, or high-grade (Gleason score ≥7) or intraductal prostate cancer at any age
     - Diagnosed at age ≤60 y with triple-negative breast cancer;
     - Diagnosed at any age with:
       - ◊ Ashkenazi Jewish ancestry; or
       - ◊ ≥1 close blood relative[e] with breast cancer at age ≤50 y or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age; or
       - ◊ ≥3 total diagnoses of breast cancer in patient and/or close blood relatives[e]
     - Diagnosed at any age with male breast cancer
   - Epithelial ovarian cancer[f] (including fallopian tube cancer or peritoneal cancer) at any age
   - Exocrine pancreatic cancer at any age[g] (See CRIT-3)
   - Metastatic or intraductal prostate cancer at any age[h]
   - High-grade (Gleason score ≥7) prostate cancer with:
     - Ashkenazi Jewish ancestry; or
     - ≥1 close relative[e] with breast cancer at age ≤50 y or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age; or
     - ≥2 close relatives[e] with breast or prostate cancer (any grade) at any age.
   - A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline
   - To aid in systemic therapy decision-making, such as for HER2-negative metastatic breast cancer[i]
4. *Family history of cancer*
   - An affected or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except individuals who meet criteria only for systemic therapy decision-making)[j]
   - An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, PennII)[k]

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Criteria met → See GENE-1

If testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

Footnotes on CRIT-2

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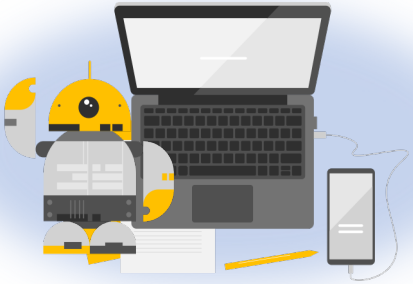
Complex guidelines are difficult to implement

Manual

vs



Automated

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Footnotes on CRIT-2

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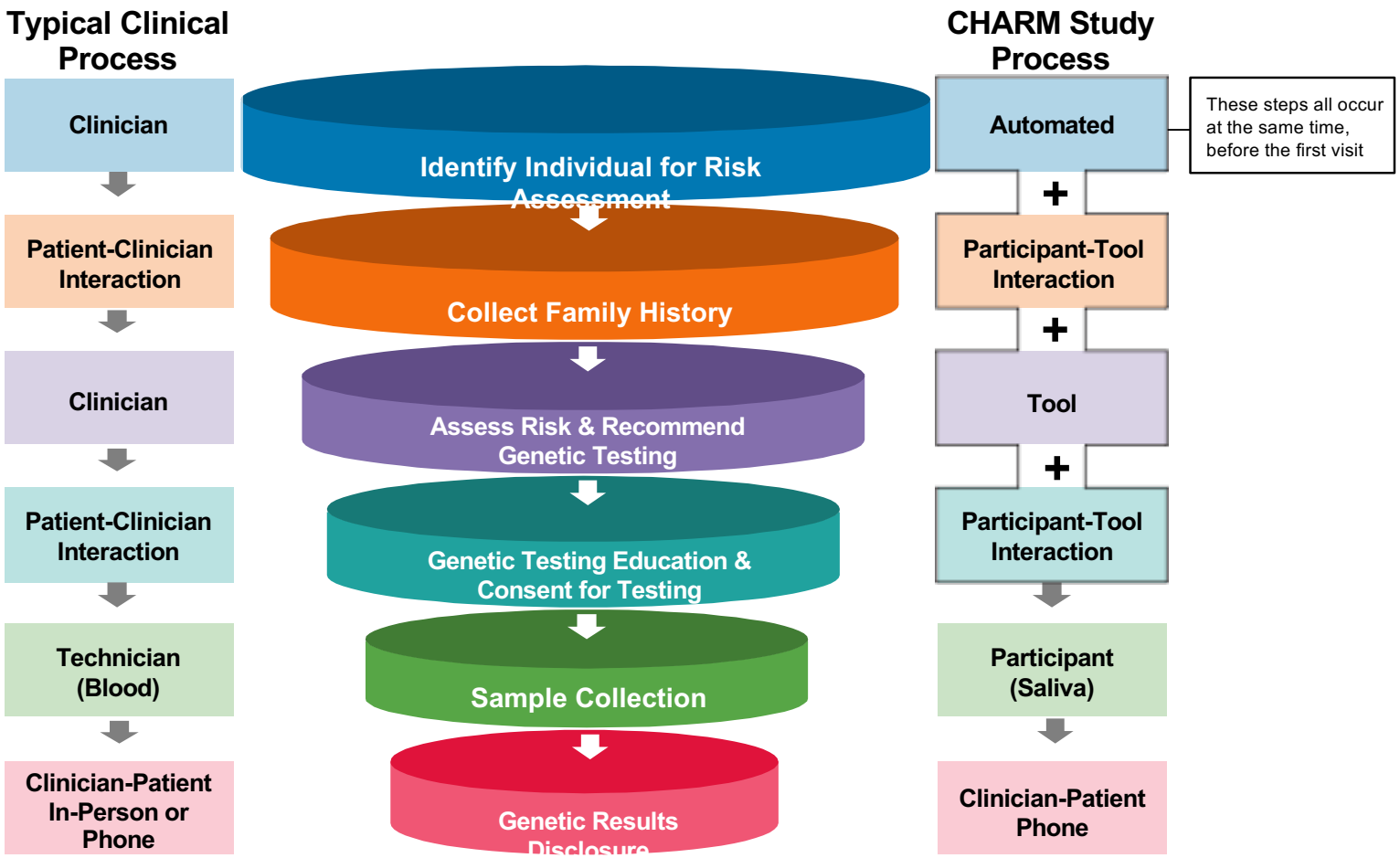

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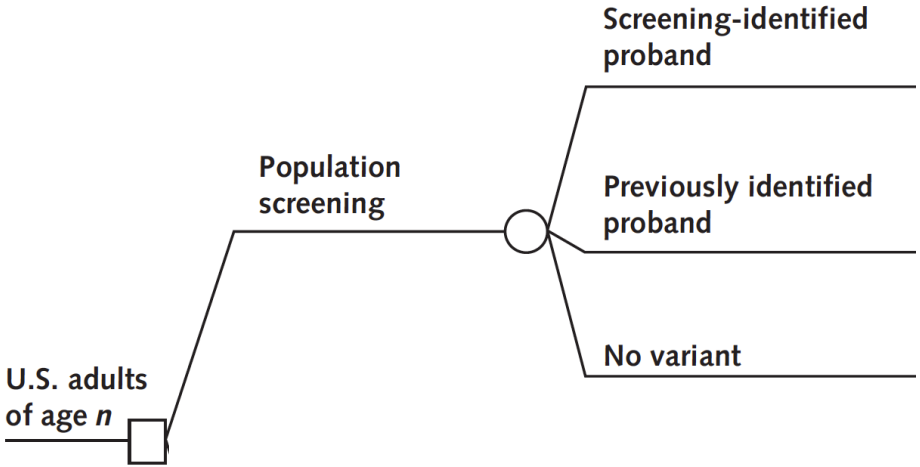
Population genetic screening for HBOC, LS and FH



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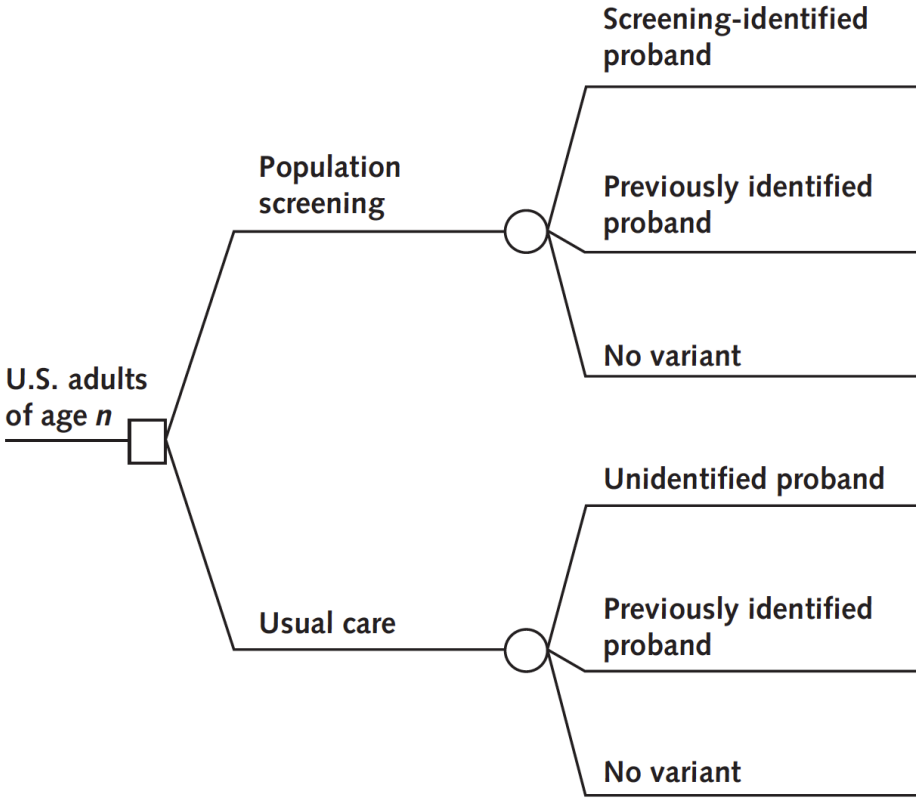

Results of Base-Case Analysis: Screening 100 000 unselected 30-year-olds resulted in 101 (95% uncertainty interval [UI], 77 to 127) fewer overall cancer cases and 15 (95% UI, 4 to 28) fewer cardiovascular events and an increase of 495 quality-adjusted life-years (QALYs) (95% UI, 401 to 757) at an incremental cost of $33.9 million (95% UI, $27.0 million to $41.1 million). The incremental cost-effectiveness ratio was $68 600 per QALY gained (95% UI, $41 800 to $88 900).

Results of Sensitivity Analysis: Screening 30-, 40-, and 50-year-old cohorts was cost-effective in 99%, 88%, and 19% of probabilistic simulations, respectively, at a $100 000-per-QALY threshold. The test costs at which screening 30-, 40-, and 50-year-olds reached the $100 000-per-QALY threshold were $413, $290, and $166, respectively. Variant prevalence and adherence to preventive interventions were also highly influential parameters.

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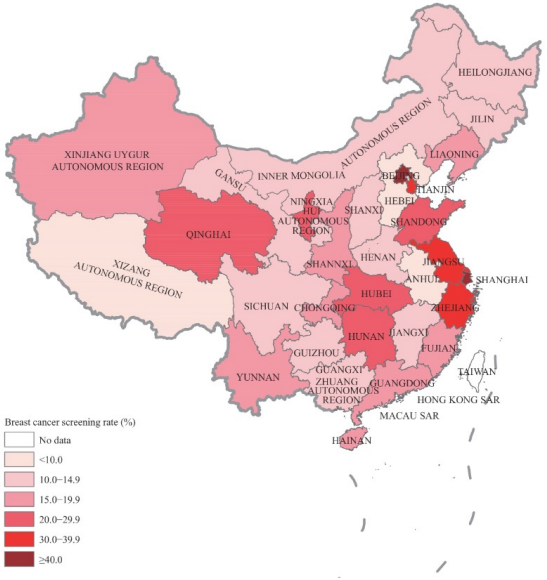
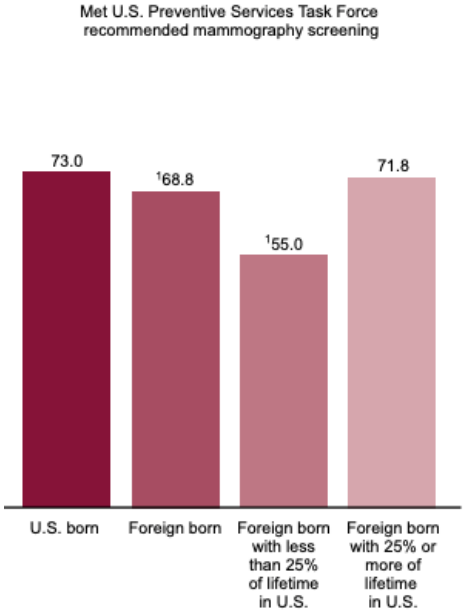
Mammography screening guidelines: coverage gaps

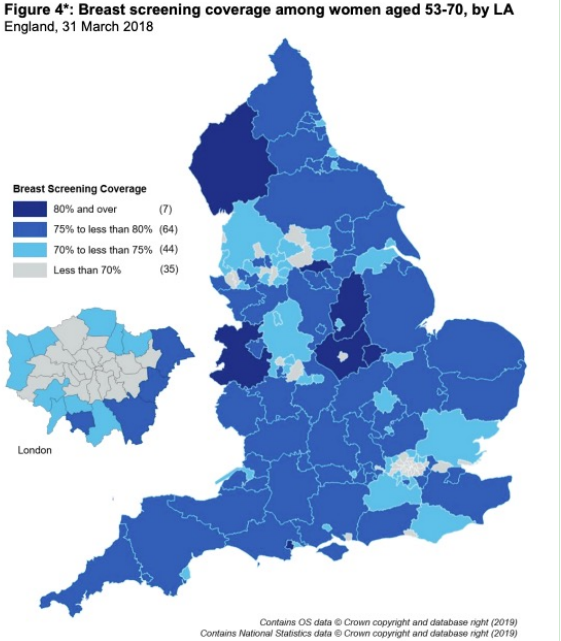
PR China



United States (USPSTF)



United Kingdom (NHS)



https://weekly.chinacdc.cn/en/article/doi/10.46234/ccdcw2021.078
https://www.cdc.gov/nchs/data/nhsr/nhsr129-508.pdf
https://files.digital.nhs.uk/60/77DCCC/breast-screening-programme-eng-2017-18-report.pdf

Sick individuals and sick populations

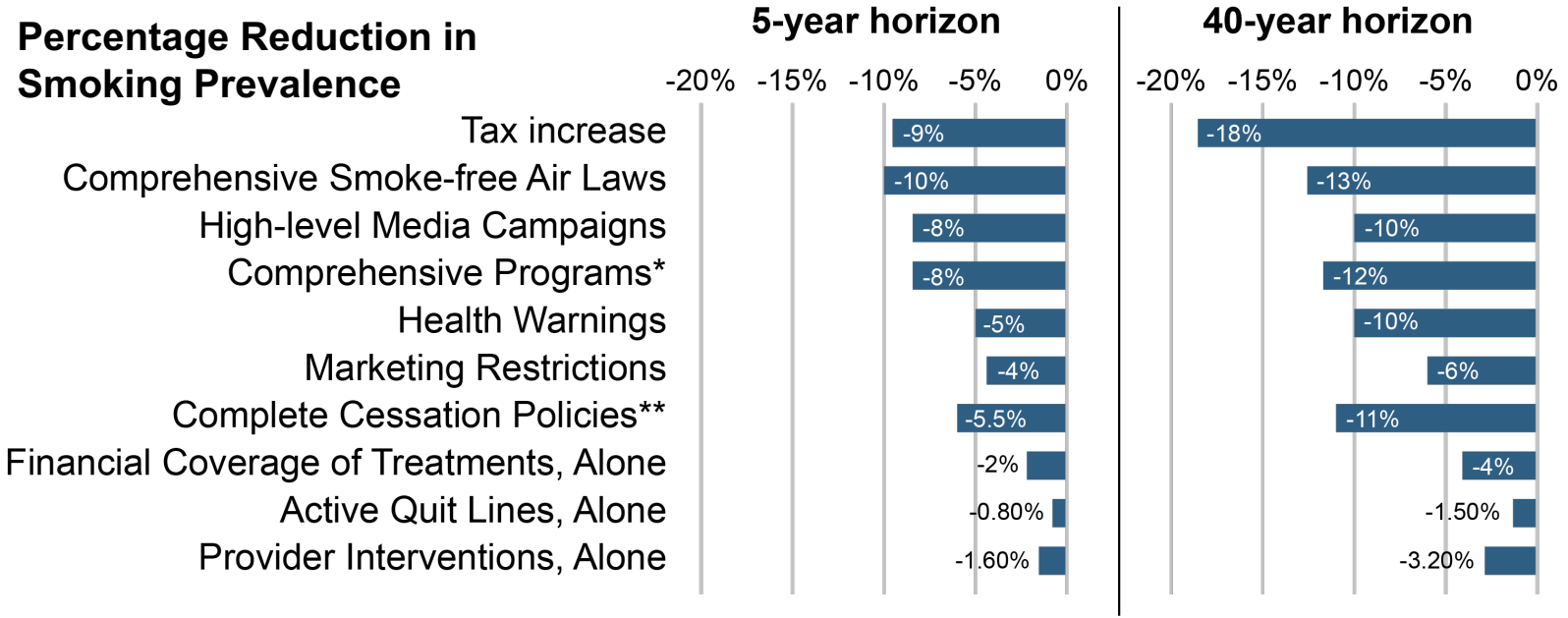
Geoffrey Rose

Rose G (Department of Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK). Sick individuals and sick populations. *International Journal of Epidemiology* 1985;**14:**32–38.

Aetiology confronts two distinct issues: the determinants of individual cases, and the determinants of incidence rate. If exposure to a necessary agent is homogeneous within a population, then case/control and cohort methods will fail to detect it: they will only identify markers of susceptibility. The corresponding strategies in control are the 'high-risk' approach, which seeks to protect susceptible individuals, and the population approach, which seeks to control the causes of incidence. The two approaches are not usually in competition, but the prior concern should always be to discover and control the causes of incidence.

Rose (1985) Int J Epidemiol

Impact of Individual level vs. Societal level Interventions in Tobacco Control



*Comprehensive programs including media, other educational and cessation programs

**Complete cessation policies include financial coverage of treatments, quit lines, and health care provider interventions

Levy et al. *J Public Health Management & Practice.* 2018;24(5):448-457.

Slide courtesy of Katrina Goddard

VIEWPOINT

Will Precision Medicine Improve Population Health?

Muin J. Khoury, MD, PhD
Office of Public Health Genomics, Centers for Disease Control and Prevention, Atlanta, Georgia.

Sandro Galea, MD, DrPH
Boston University School of Public Health, Boston, Massachusetts.

Announcement of the precision medicine initiative has led to a variety of responses, ranging from enthusiastic expectations[1] to explicit skepticism,[2] about potential health benefits, limitations, and return on investment. This Viewpoint discusses whether precision medicine is unlikely or likely t
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individuals is not a
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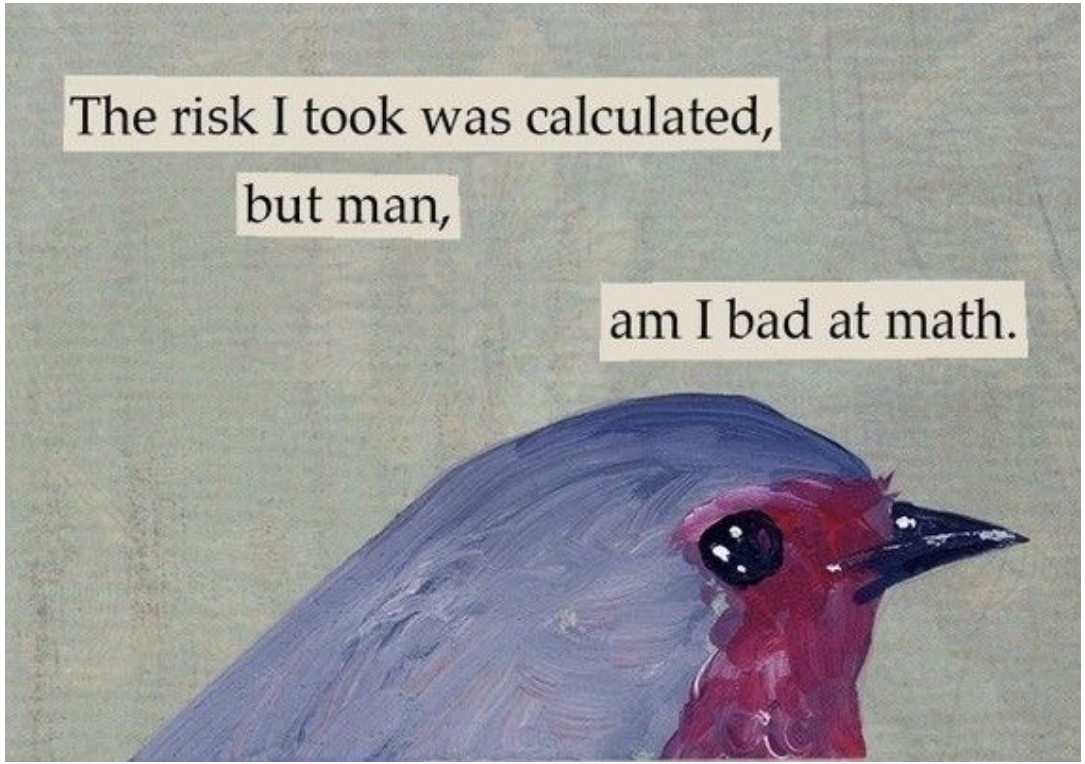
It is, in fact, more likely that a combination of approaches—ranging from population-wide interventions to specific interventions tailored to higher-risk groups—will be required to efficiently improve population health and narrow health disparities.

Khoury and Galea (2016) JAMA



Thank you!

Questions?

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