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From genomics to stratified, population based cancer screening

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Recommendations from the Collaborative Oncological Gene-environment Study (COGS 2014) – 7° EU Framework Programme
Aims and objectives

1. Use the results of primary research into gene-disease association, gene-environment interaction and individual risk prediction models to evaluate the potential for stratification of the population according to individual risk of breast, ovarian and prostate cancer
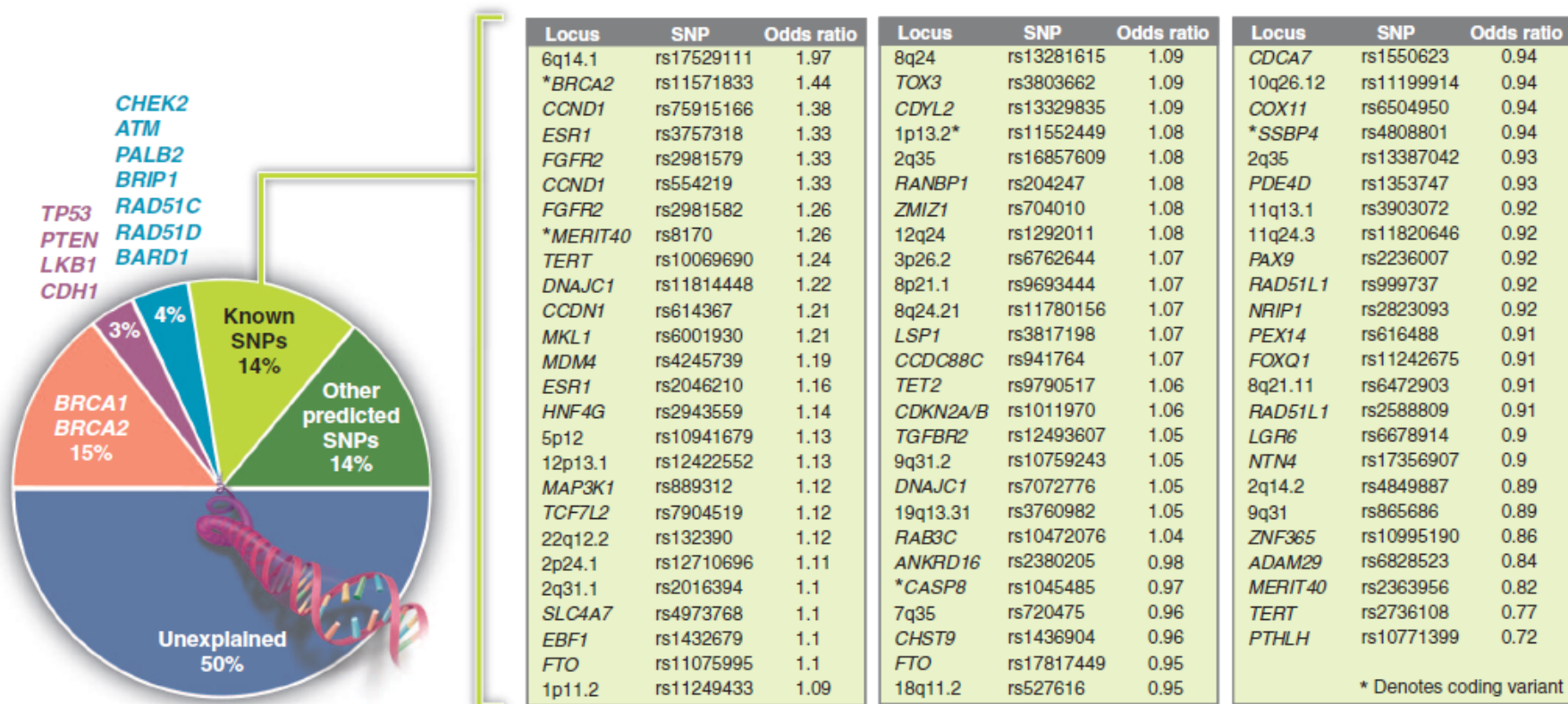
Fig. 1. Genetic variants that predispose to breast cancer. The pie chart on the left shows the estimated percentage contribution of mutations in high-penetrance (*BRCA1/2*, *TP53*, *CDH1*, *LKB1*, and *PTEN*) and moderate-penetrance (e.g., *CHEK2*, *ATM*, and *PALB2*) genes and common low-penetrance genetic variants to familial relative risk. Common genetic variants are denoted as SNPs. "Known SNPs" are SNPs associated with breast cancer through GWAS, as listed on the right. The odds ratios refer to the increase (or, in some cases, the reduction) in risk conferred by the rare allele of the variants. "Other predicted SNPs" refers to the estimated contribution of all SNPs, other than known loci, that were selected for replication of breast cancer GWAS (5, 39).

FJ Couch *et al.*, 2014
Science

Personalized screening of breast cancer

- Reproductive history, life styles, metabolic syndrome
- Breast density
- Genetic variants

Breast Cancer Risk Assessment Tool (BCRAT)

- **The NCI's BCRAT or "Gail Model 2"**
    - **Risk factors in BCRAT**
        - **Age**
        - **Age at first live birth**
        - **Age at menarche**
        - **Number of mother/sisters with breast cancer**
        - **Number of previous benign breast biopsies and whether atypical hyperplasia present on any**

ROC curves for Gail, Claus, Ford (BRCAPro), Tyrer-Cuzick and the Manual models

ROC Curve

Source of the Curve
- Reference Line
- Gail
- Claus
- Ford
- Tyrer-Cuzick
- Manual
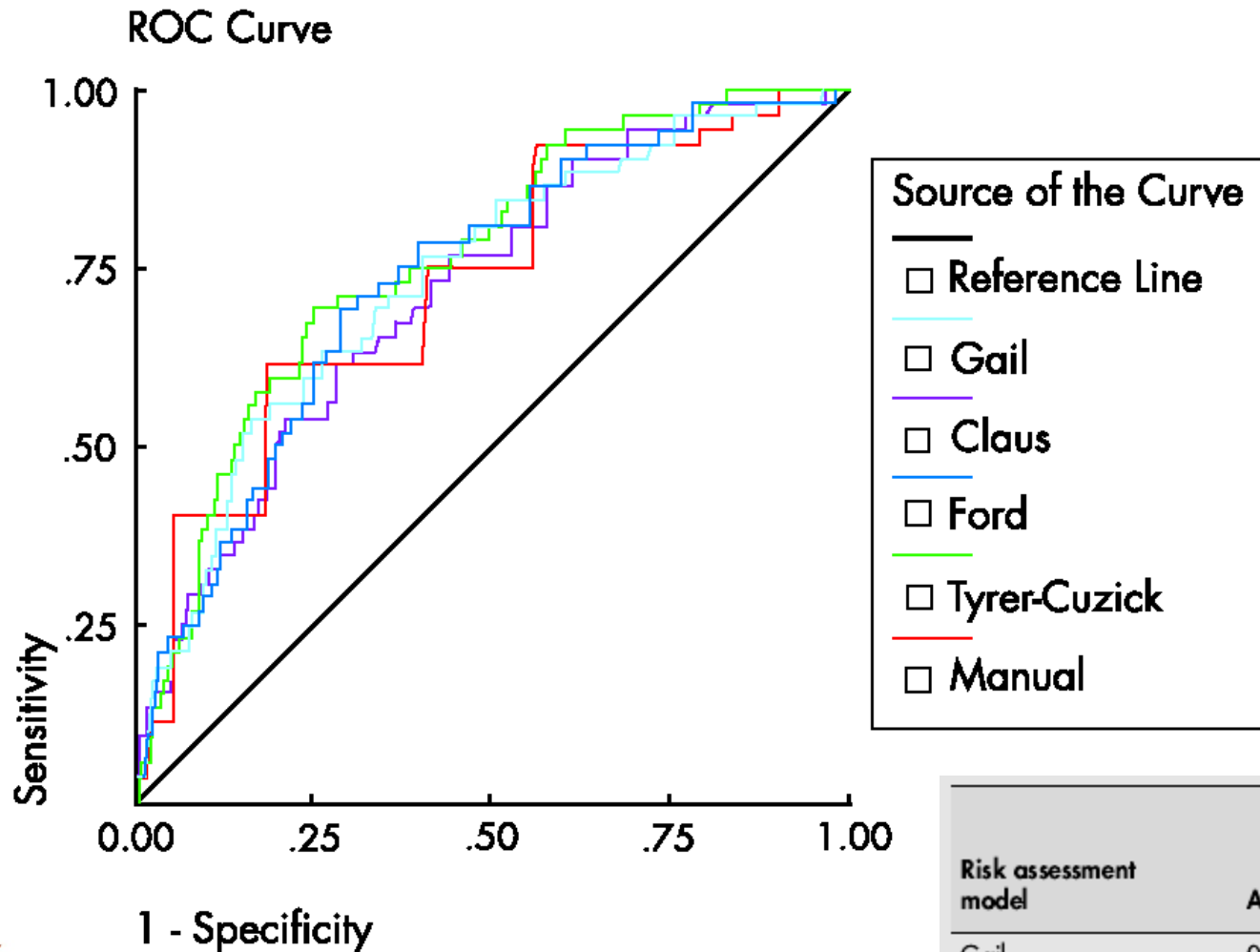
Risk assessment model	Area	Asymptotic 95% confidence interval	
		Lower bound	Upper bound
Gail	0.735	0.666	0.803
Claus	0.716	0.648	0.784
Ford	0.737	0.671	0.803
Tyrer–Cusick	0.762	0.700	0.824
Manual	0.727	0.656	0.798

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Table 2. Percentage and relative risks for promoters affecting the transition rate from the pre-clinical screen-detectable phase (PCDP) to the clinical phase (CP)

Variables	Percentage (%) of breast cancer in the PCDP (pre-symptomatic cases)	Relative risk of the progression from the PCDP to the CP (symptomatic cases)	References
BMI (kg m^{-2})			
≤23	26.20[a]	1.00	Hsieh et al, 2002
>23	73.80[a]	2.00	Chen et al, 2004
Age at full-term first pregnancy (years)			
≤25	57.62[a]	1.00	Hsieh et al, 2002
>25	42.38[a]	1.56	Chen et al, 2004
ER status			
Positive	81.00	1.00	Dong et al, 2008
Negative	19.00	1.35	
Ki-67 proliferation			
<10%	30.1	1.00	Dong et al, 2008
10–30%	50.7	1.40	
>30%	19.2	2.11	
HER-2/*neu* immunohistochemistry score			
0 or 1+	75.6	1.00	Dong et al, 2008
2+	11.9	1.28	
3+	12.5	1.07	

[a]These values are based on the simulated PCDP (pre-symptomatic cases) simulated from free of breast cancer to the PCDP following the distribution of women free of breast cancer in Table 1.

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2. Evaluate the potential of stratified prevention to reduce the incidence of and the mortality from these cancers by risk stratification and targeting of population-based screening and **prevention programmes**, including cost-effectiveness analysis

Diet
Physical exercize
Metabolic syndrome

Preventive intervention on lifestyle factors

Risk Factor Modification and Projections of Absolute Breast Cancer Risk

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Background	Although modifiable risk factors have been included in previous models that estimate or project breast cancer risk, there remains a need to estimate the effects of changes in modifiable risk factors on the absolute risk of breast cancer.
Methods	Using data from a case–control study of women in Italy (2569 case patients and 2588 control subjects studied from June 1, 1991, to April 1, 1994) and incidence and mortality data from the Florence Registries, we developed a model to predict the absolute risk of breast cancer that included five non-modifiable risk factors (reproductive characteristics, education, occupational activity, family history, and biopsy history) and three modifiable risk factors (alcohol consumption, leisure physical activity, and body mass index). The model was validated using independent data, and the percent risk reduction was calculated in high-risk subgroups identified by use of the Lorenz curve.
Results	The model was reasonably well calibrated (ratio of expected to observed cancers = 1.10, 95% confidence interval [CI] = 0.96 to 1.26), but the discriminatory accuracy was modest. The absolute risk reduction from exposure modifications was nearly proportional to the risk before modifying the risk factors and increased with age and risk projection time span. Mean 20-year reductions in absolute risk among women aged 65 years were 1.6% (95% CI = 0.9% to 2.3%) in the entire population, 3.2% (95% CI = 1.8% to 4.8%) among women with a positive family history of breast cancer, and 4.1% (95% CI = 2.5% to 6.8%) among women who accounted for the highest 10% of the total population risk, as determined from the Lorenz curve.
Conclusions	These data give perspective on the potential reductions in absolute breast cancer risk from preventative strategies based on lifestyle changes. Our methods are also useful for calculating sample sizes required for trials to test lifestyle interventions.

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3.Identify the key organisational, ethical, legal and social issues that would arise from such targeted screening and other prevention programmes and make appropriate policy recommendations

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Methods

- **Modelling**
  1. Estimate of the proportion of the population with a polygenic risk of diagnosis greater than a given threshold, and the proportion of cases that will occur in this subgroup:
     - Breast cancer: risk threshold 2.5% over 10 yrs
     - Prostate cancer: risk threshold 2% over 10 yrs
  2. Comparison of screening based on age alone with screening based on polygenic profile

Polygenic susceptibility to prostate and breast cancer: implications for personalised screening

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BACKGROUND: We modelled the efficiency of a personalised approach to screening for prostate and breast cancer based on age and polygenic risk-profile compared with the standard approach based on age alone.

METHODS: We compared the number of cases potentially detectable by screening in a population undergoing personalised screening with a population undergoing screening based on age alone. Polygenic disease risk was assumed to have a log-normal relative risk distribution predicted for the currently known prostate or breast cancer susceptibility variants ($N = 31$ and $N = 18$, respectively).

RESULTS: Compared with screening men based on age alone (aged 55–79: 10-year absolute risk $\geqslant 2\%$), personalised screening of men age 45–79 at the same risk threshold would result in 16% fewer men being eligible for screening at a cost of 3% fewer screen-detectable cases, but with added benefit of detecting additional cases in younger men at high risk. Similarly, compared with screening women based on age alone (aged 47–79: 10-year absolute risk $\geqslant 2.5\%$), personalised screening of women age 35–79 at the same risk threshold would result in 24% fewer women being eligible for screening at a cost of 14% fewer screen-detectable cases.

CONCLUSION: Personalised screening approach could improve the efficiency of screening programmes. This has potential implications on informing public health policy on cancer screening.

Table 3 Reclassification of population of 100 00 women 35–79 years eligible for screening and in whom breast cancer could be detectable, under age-based or personalised screening strategies.

Personalised screening Polygenic risk threshold	Age-based screening		
	<47 years	≥47 years	Total
Population			
<2.5%	30 276	19 926	50 202
≥2.5%	4429	45 368	49 798
Total	34 705	65 295	100 000
Cases			
<2.5%	26	38	64
≥2.5%	9	162	172
Total	35	200	236

Eligibility based on age 47 or polygenic risk equivalent to 10-year absolute risk for age 47 (2.5% 10-year absolute risk); England 2002–2006.

Personalized screening for women 35-79 yrs at 2.5% in 10yrs risk threshold would result in 24% fewer women eligible for screening and 14% fewer detectable cases compared with screening women based on age 47- 79 alone

Potential advantages

- It might reduce the number of people needing to be screened to achieve the same preventive impact

- It might increase the preventive impact from the screening the same number of people

- It might permit different screening approaches to be used in people with different risks, matching benefits and risks more precisely

Overdiagnosis

Duffy SW et al. (2010)	the diagnosis of a cancer as a result of screening that would not have been diagnosed if in the woman's lifetime had screening not taken place

For every 10000 women <u>screened</u> since age 50 for 20 years:

	EUROSCREEN review (screening interval 2 years, follow up till age 79)	UK Independent review (screening interval 3 years)
Cases diagnosed	**710**	
BC deaths expected	**300** **(190 IBM)**	
Lives saved	**80**	**56**
Over-diagnosed cases	**40**	**168**
LS : OD	**1 : 0.5**	**1 : 3**

Stratified Cancer Screening: The Practicalities of Implementation.

Dent T, Jbilou J, Rafi I, Segnan N, Törnberg S, Chowdhury S, Hall A, Lyratzopoulos G, Eeles R, Eccles D, Hallowell N, Pashayan N, Pharoah P, Burton H.

Implementation issues

- Countries with organised screening that is delivered using population databases are potentially able to offer screening programmes according to the estimated risk of the participant; those that rely on opportunistic approaches may find it more difficult

- The selection of interventions should be based on good evidence of effectiveness, including the balance of benefit and harm for the different risk groups and relevant costs, but little such evidence yet exists

- Where there is an established screening programme, such as for breast cancer, there may be political or public resistance to a reduction of the screening offered to low-risk groups

- If the use of genomic information to stratify population entails the retention of samples and data for diverse uses for many years, it will give rise to many ethical, legal and social concerns

Figure. Percentage of breast cancer mortality reduction versus number of mammographies performed per 1000 women, by model and screening strategy.
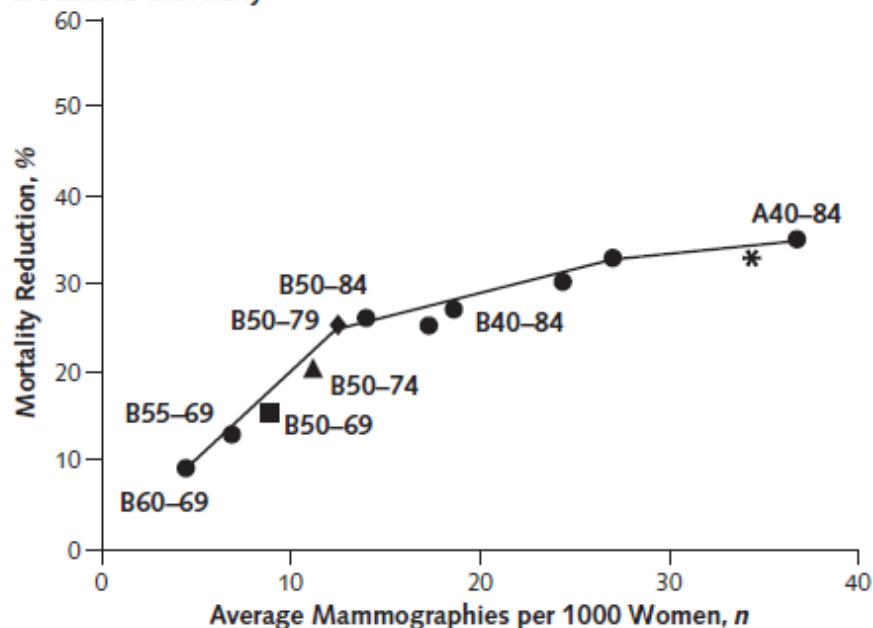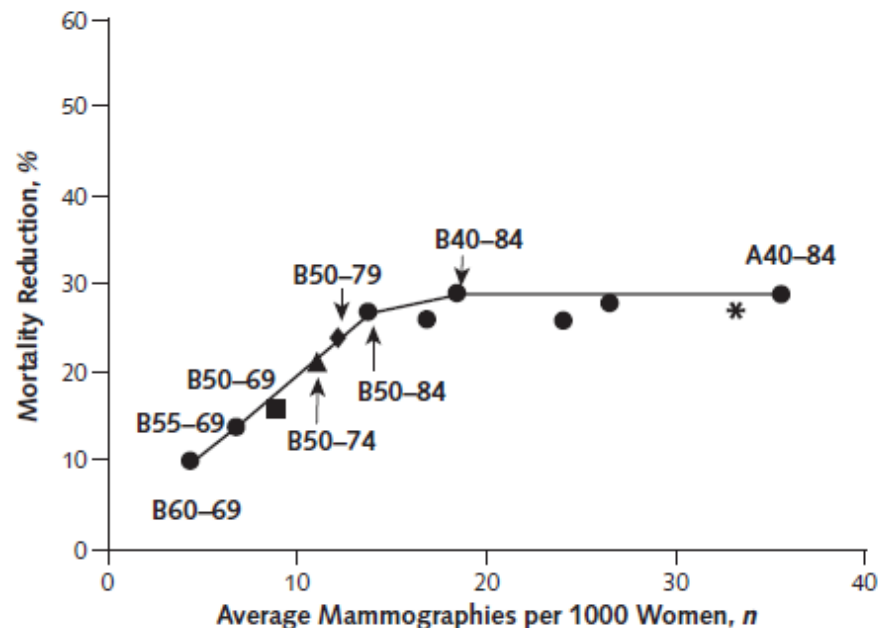
JS Mandelblatt *et al.*, 2009

Annals Internal Medicine

COGS Recommendations

1. Effectiveness of risk-stratified screening

1.1 We recommend that stratified screening should not be implemented until further empirical evidence is available about whether a risk-based screening approach improves the benefit-harm balance of screening for prostate and breast cancer

1.2 If further research indicates that risk-stratified screening improves the benefit-harm balance of screening, then we recommend decision modelling to identify the optimum screening strategy for breast and prostate cancer

1.3 Before implementing the optimum risk-based screening strategy, we recommend investigation of the feasibility of implementation.

2. Delivery

We recommend that:

2.1 The implementation of stratified screening is tailored to the organisation of health services in the country in question

2.2 Policy-makers develop detailed plans for the delivery of stratified screening, giving attention to the issues in Appendix 2

2.3 Policy-makers develop sound quality assurance systems to maximise benefits and minimise harms

2.4 Policymakers develop and articulate clear policies on risk stratification, particularly where the purpose is targeting of limited resources

2.5 Research into the impact of technological change on the delivery of stratified cancer screening is instigated.

3. Ethical, legal and social issues

3.1 In the short term, we recommend that any risk-stratified programme that is introduced has a specific clearly defined purpose, and that the storage and linkage of samples and data are minimised.

We recommend that:

3.2 More comprehensive programmes genotyping multiple conditions involving lifetime storage of samples or data should not currently be introduced

3.3 Personalised screening is restricted to adult populations. We do not support the systematic genotyping of newborns or young children as a preliminary to risk assessment

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3.4 The consent process should address the benefits, harms and uncertainties of genotyping and risk assessment, the precise nature of which will be dependent on context. Where possible, we recommend the use of an encompassing consent which takes account of reasonable and foreseeable future developments

3.5 Providers of risk stratification incorporating a genotypic element should be transparent about the evidence base and quality assurance processes that are used, to ensure that, regardless of provider, the risk assessments that are generated are safe, robust and evidence-based

3.6 Decision-making should be fully inclusive, ensuring meaningful engagement of all stakeholders in the policy-making process

3.7 Research to clarify the wider ethical, legal and social impact of stratifying on the basis of genotypic and phenotypic risk, as compared with determinants such as age, sex and ethnic group is undertaken. In particular, we recommend research to clarify the potential for generating inequalities relating to distributive justice

3.8 Comprehensive conceptual and empirical research into the impact of ethnic and cultural factors on understanding, acceptability and uptake of personalised screening is undertaken.

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4. Professional education and training and public understanding

We recommend that:

4.1 Health care professionals are prepared for the use of genomics in common disease prevention including risk-stratified screening, building on existing knowledge and skills. We recommend formal educational needs assessment as a prerequisite for implementation.

5. Public understanding and acceptability

5.1 We recommend research on public understanding of risk stratified screening and its acceptability to the public before risk stratified screening is implemented.

Thank you for the attention