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Sir Richard Doll Seminar

The Risk of Everything

March 2020

Professor Julia Hippisley-Cox

Professor of Clinical Epidemiology & GP

Professorial Fellow St Anne's

University of Oxford

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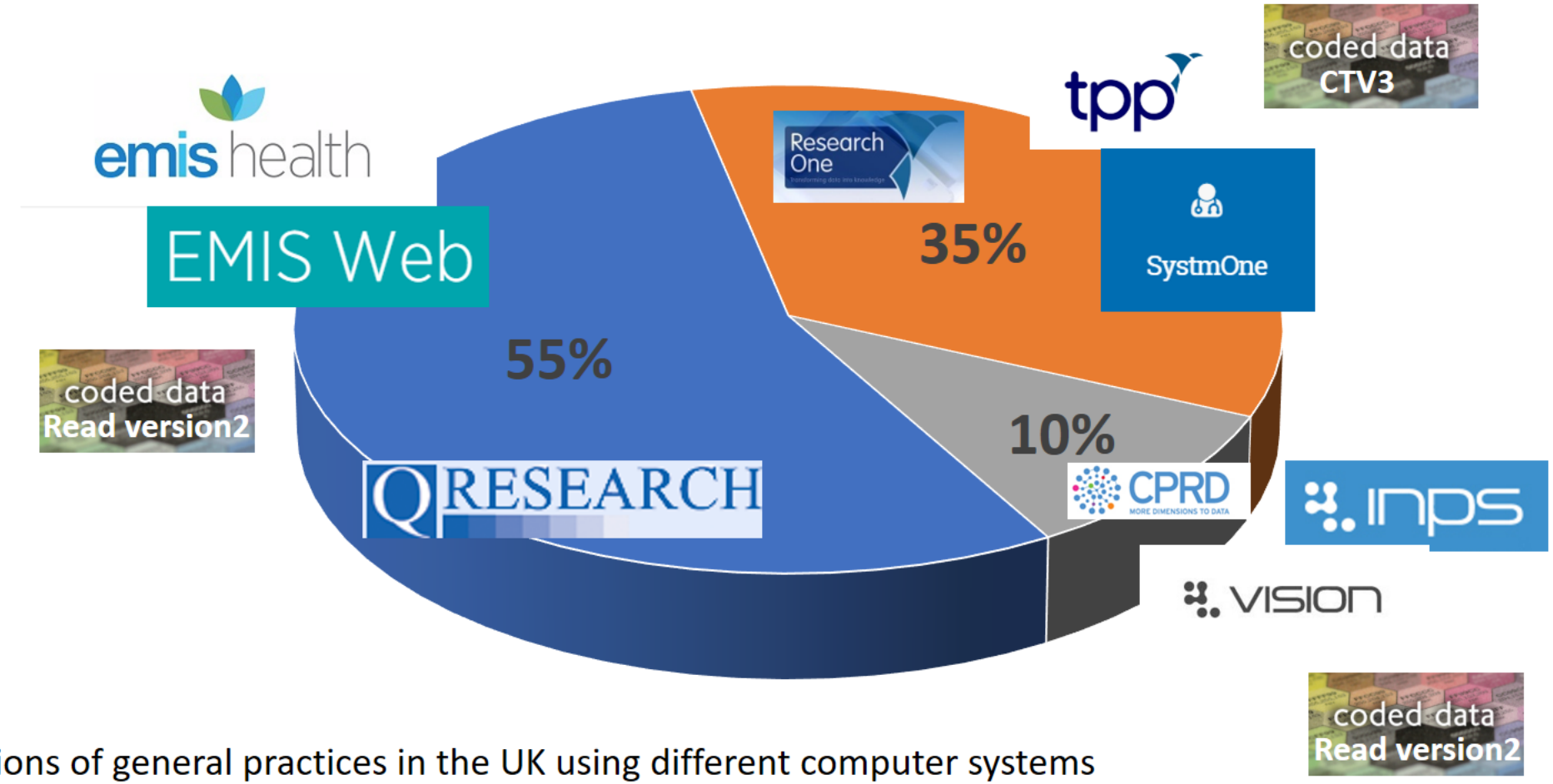
JHC Roles & Disclosures

- Prof Clinical Epidemiology and GP
- NHS GP Woodstock Surgery
- Director QResearch (non-profit venture with EMIS Health)
- Founder & former director ClinRisk Ltd (software company which produces open and closed source software).
- Trustee EMIS National User Group (medical research charity)
- Director QSurveillance database – infectious diseases

Talk Outline

- The QResearch Database
- Risk Prediction tools - what are they and why are they useful?
- QRISK3 – heart disease
- QCancer – early identification, screening cancer
- Next steps

Primary care data collection in the UK



Proportions of general practices in the UK using different computer systems

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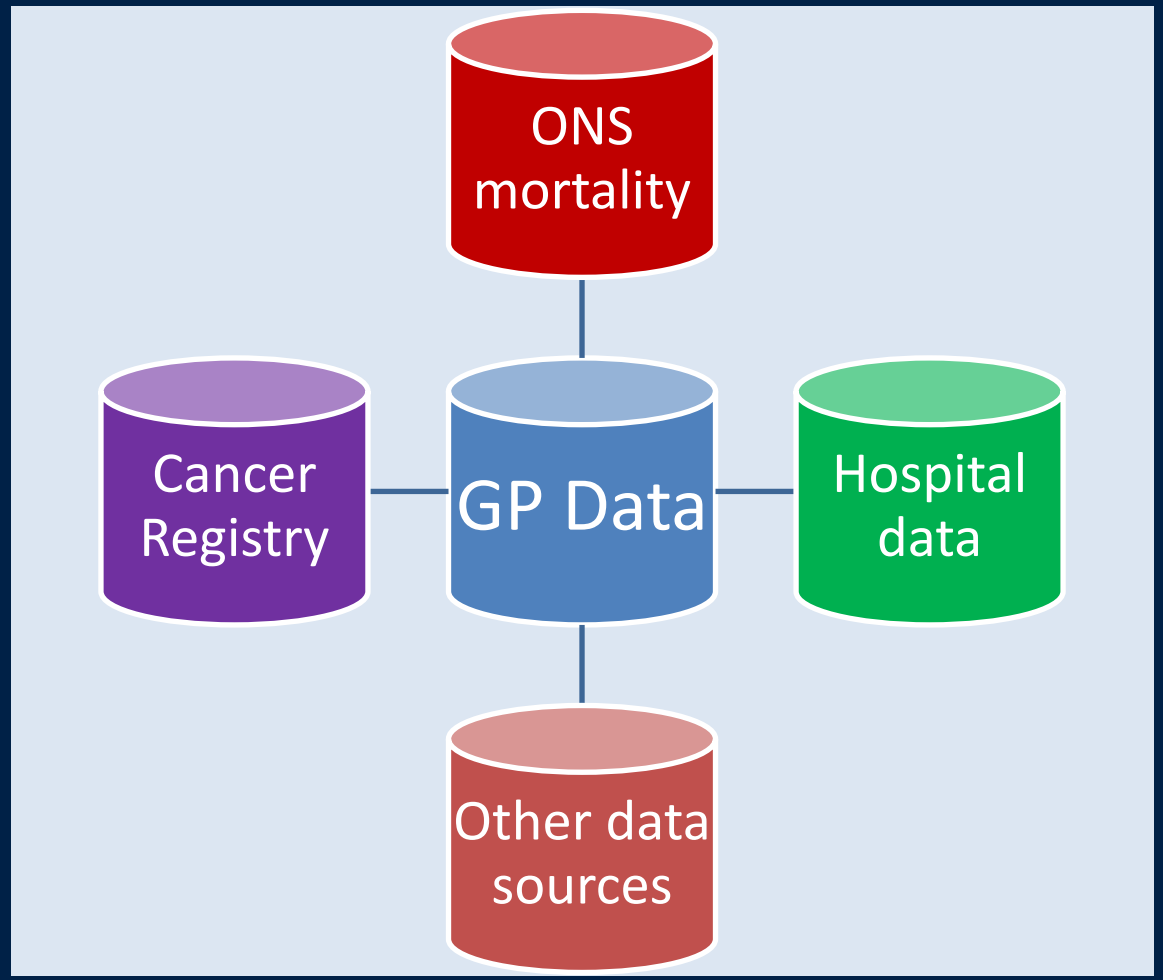
- QResearch database founded in 2003
- Collaboration with EMIS Health
- Anonymised data from > 1500 practices
- Individual data > 30 million patients
- Historical Data > 25 years
- World beating resource for innovative medical research



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GP Data

- Demographics
- Prescriptions
- Diagnoses
- Lab investigations
- Clinical values
- Consultations
- Symptoms
- referrals

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HES Data

- Admissions
- A&E episode
- Outpatients
- Critical Care
- Maternity
- Operations (OPCS)
- Some diagnostics

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Cancer registry

- Date diagnosis
- Type cancer
- Morphology
- Grade
- Stage
- Route to diagnosis
- Treatment
- Size

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Cancer registry

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- Route to diagnosis
- Treatment
- Size

Mortality

- Date of death
- Up to 15 causes death
- ICD10 codes

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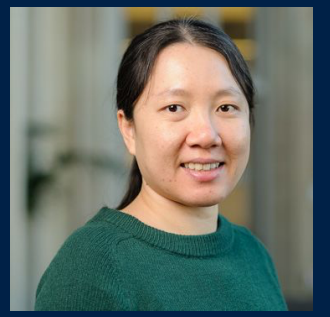
- QResearch is now an Oxford Resource.
- Infrastructure Support Oxford CRUK and ISSF Wellcome to increase access/develop Centre for Prediction modelling
- Online Application form
- Data Dictionaries www.qresearch.org
- Science Committee Chair Rafael Perera
- Building up Show Case
- Delighted to hear from anyone wishing to use database






qresearch@phc.ox.ac.uk

Summary Analysis of QResearch Linked Cancer Datary of GP population characteristics

Numbers of cancer registrations linked to QResearch 1990-2017

The table below shows the numbers of new (incident) cancer diagnoses from the National Cancer Registry which are linked to patients on version 43 of QResearch compared with National Data from England 01.01.1990 to 31.12.2017. The distribution of the types of cancers, shown by the column percent, is similar in QResearch and across England.

For more information about types of cancer visit CRUK website or the Patient.Info Website or click on the hyperlinks below.

Type of cancer (link goes to further information about the type of cancer)	QResearch Cases	percentage of all cancers on QResearch	total in England	percentage of all cancers in England
Skin cancer (excluding melanoma)	251,124	22.4	2,050,847	20.5
Breast cancer	112,401	10.0	1,015,410	10.1
Breast cancer (in situ)	12,743	1.1	103,081	1.1
Prostate cancer	93,496	8.3	786,900	7.9
Lung cancer	92,712	8.3	901,024	9.0
Colorectal cancer	90,156	8.0	821,153	8.2
Cervical cancer in situ	53,650	4.8	556,130	5.6
Malignant melanoma incl insitu	37,482	3.3	298,279	3.0
Kidney cancer	30,935	2.8	257,274	2.6
Non-Hodgkins Lymphoma	27,561	2.5	240,593	2.4
Bladder Cancer	26,163	2.3	256,078	2.6
Leukaemia	20,804	1.9	185,481	1.9
Pancreatic cancer	19,868	1.8	179,395	1.8
Oesophageal cancer	18,813	1.7	170,025	1.7
Uterine cancer	18,026	1.6	156,033	1.6
Stomach (Gastric) cancer	18,020	1.6	188,543	1.9
Mouth (oral) cancer	17,832	1.6	154,348	1.5

Representative Distribution of Patients across England

Overall, there are almost 35 million patient records on QResearch (version 43) between 1990 and 2018, from 1616 GP practices. This includes those who have died (2.15million), left the practice (19.54 million) and those who are still registered (13.10 million). 51.6% are women and 48.4% are men. The patients are spread throughout 10 geographical areas in England as shown in the table below.

East Midlands	1.54 million
East of England	1.67 million
London	9.23 millon
North East	0.99 million
North West	5.07 million
South Central	4.5§ million
South East	3.16 million
South West	3.49 million
West Midlands	3.47 million
Yorkshire and humber	1.65 million

Ethnically diverse population

The database contains a rich diversity of ethnic groups (using the ethnicity which patients have assigned for themselves). This is important as it enables us to look at how different diseases may

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Developing and Validating Risk Prediction tools

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Risk Prediction Tools: research since 2007

- Developed, validated and implemented suite of widely used novel risk prediction tools

  - ❖ Prognostic - Risk of future disease e.g. CVD or cancer
  - ❖ Diagnostic - Risk of current cancer
  - ❖ Outcomes - Prognosis following cancer diagnosis

- Enables informed consent - improved risk communication
- Enables risk stratification – target resources to highest risk most likely to benefit from interventions

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Risk of Multiple Outcomes

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- QRISK3
- QStroke
- QDiabetes
- QFrailty
- QMortality
- QAdmissions
- QBleed
- QThrombosis
- QFracture
- QKidney

- QCancer – current cancer
- QCancer – 10-year risk of cancer
- QCancer – prognosis for patients with colorectal cancer

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QRISK METHODOLOGY

- Design – prospective open cohort study
- Setting – general practices in England
- Patients - without existing CVD and free from statins
  - 7.89 million in derivation cohort
  - 2.67 in validation cohort
- Outcome - incidence CVD (CHD, MI, Angina, Stroke or TIA)
- Predictors
- Analysis - Cox regression to derive separate risk equation
- Annual updates as
  - Populations change
  - Data improves
  - Technology improves

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QRISK Timeline

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2007

Project Start

Build risk algorithm to estimate CVD risk

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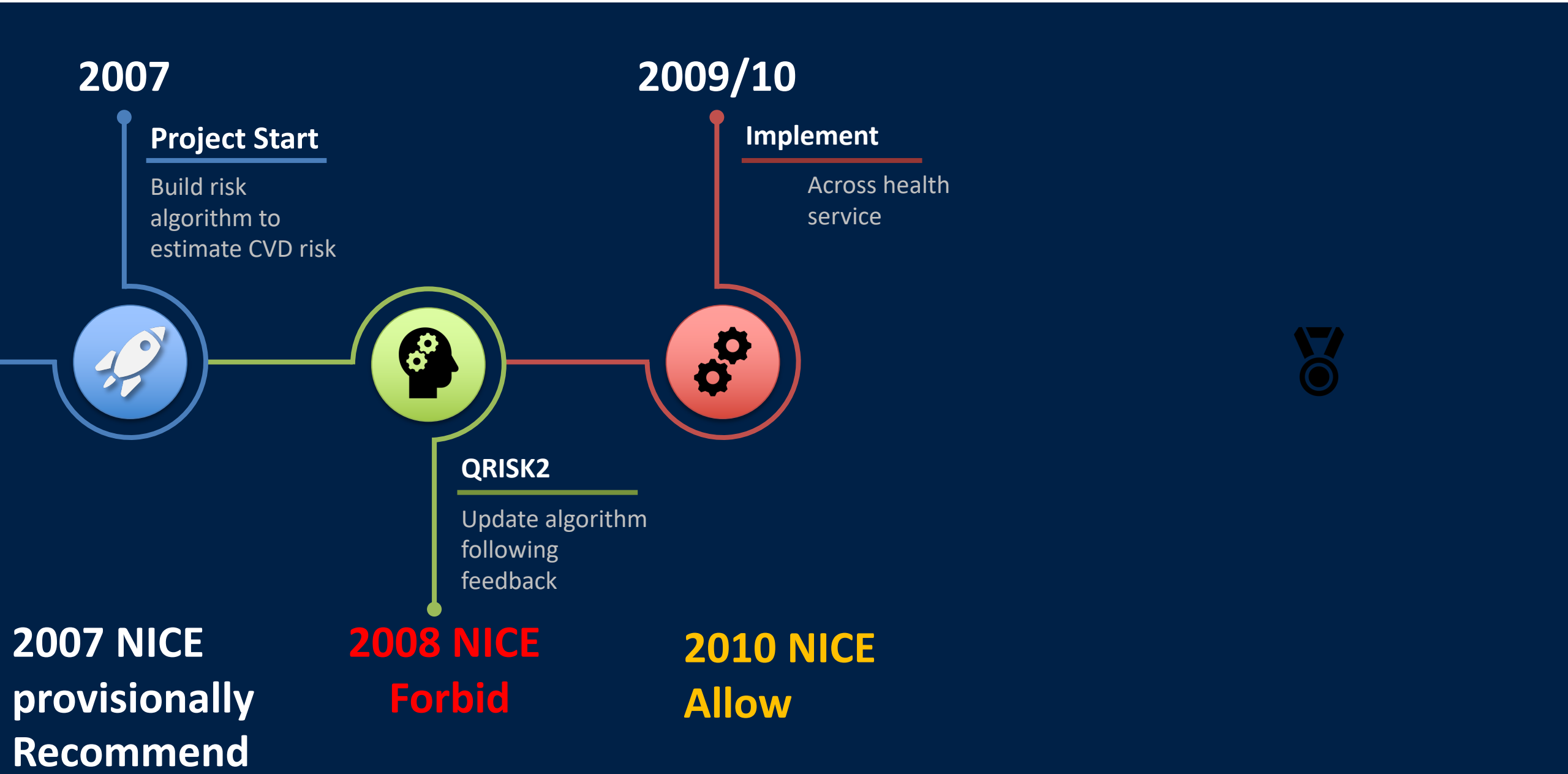

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2009/10

Implement

Across health service

2010 NICE Allow

2014

Guidelines updated

NICE recommended instead of Framingham

2014 NICE mandate

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2017

QRISK3

Updated with 8 extra risk factors

2019 NHS health checks

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QRISK IN THE BMJ

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BMJ **RESEARCH**

Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study

BMJ **RESEARCH**

Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2

thebmj Research Education News & Views Campaigns Archive

Research

Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database

BMJ 2010 ; 341 doi: https://doi.org/10.1136/bmj.c6624 (Published 09 December 2010)
Cite this as: *BMJ* 2010;341:c6624

Article | Related content | Metrics | Responses | Peer review

Julia Hippisley-Cox, professor of clinical epidemiology and general practice [1],
Carol Coupland, associate professor in medical statistics [1], *John Robson, senior lecturer general practice* [2],
Peter Brindle, research and evaluation programme director [3]

thebmj Research Education News & Views Campaigns

Research

Predicting the 10 year risk of cardiovascular disease in the United Kingdom: independent and external validation of an updated version of QRISK2

BMJ 2012 ; 344 doi: https://doi.org/10.1136/bmj.e4181 (Published 21 June 2012)
Cite this as: *BMJ* 2012;344:e4181

Article | Related content | Metrics | Responses | Peer review

Gary S Collins, senior medical statistician, Douglas G Altman, director and professor

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Research

Development and validation of QRISK3 risk prediction algorithms to estimate f risk of cardiovascular disease: prospective cohort study

BMJ 2017 ; 357 doi: https://doi.org/10.1136/bmj.j2099 (Published 23 May 2017)
Cite this as: *BMJ* 2017;357:j2099

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Carol Coupland, professor of medical statistics in primary care [1],
Peter Brindle, evaluation and implementation theme lead, NIHR CLAHRC West [2]

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QRISK3 NATIONAL GUIDELINES

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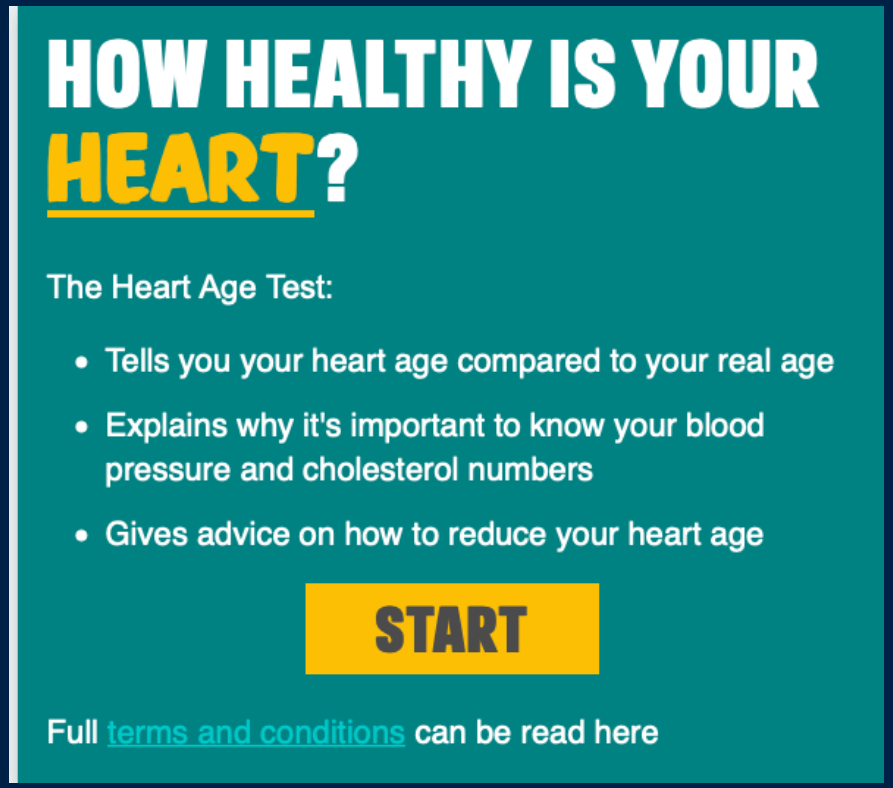
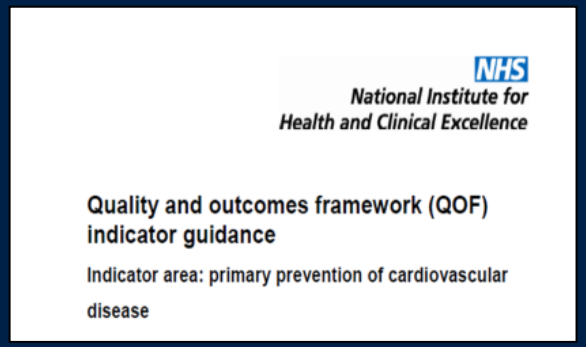
NICE Pathways | NICE guidance | Standards and indicators | Evidence search | BNF | BNFC | CKS | Journals an

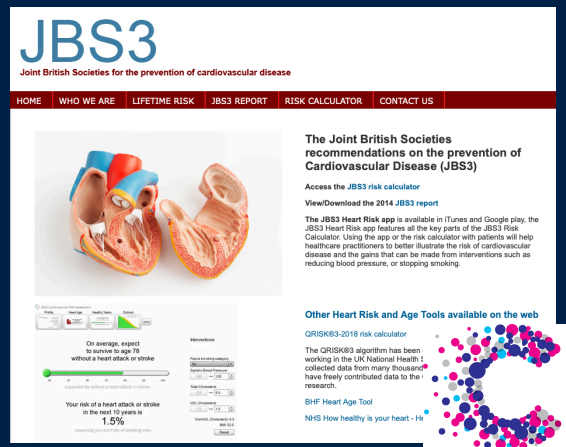
Home › NICE Guidance › Conditions and diseases › Cardiovascular conditions › Acute coronary syndromes

Cardiovascular disease: risk assessment and reduction, including lipid modification

Clinical guideline [CG181] Published date: July 2014 Last updated: September 2016 Uptake of this guidance







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QRISK INTERNATIONAL

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All Users
100.00% Users

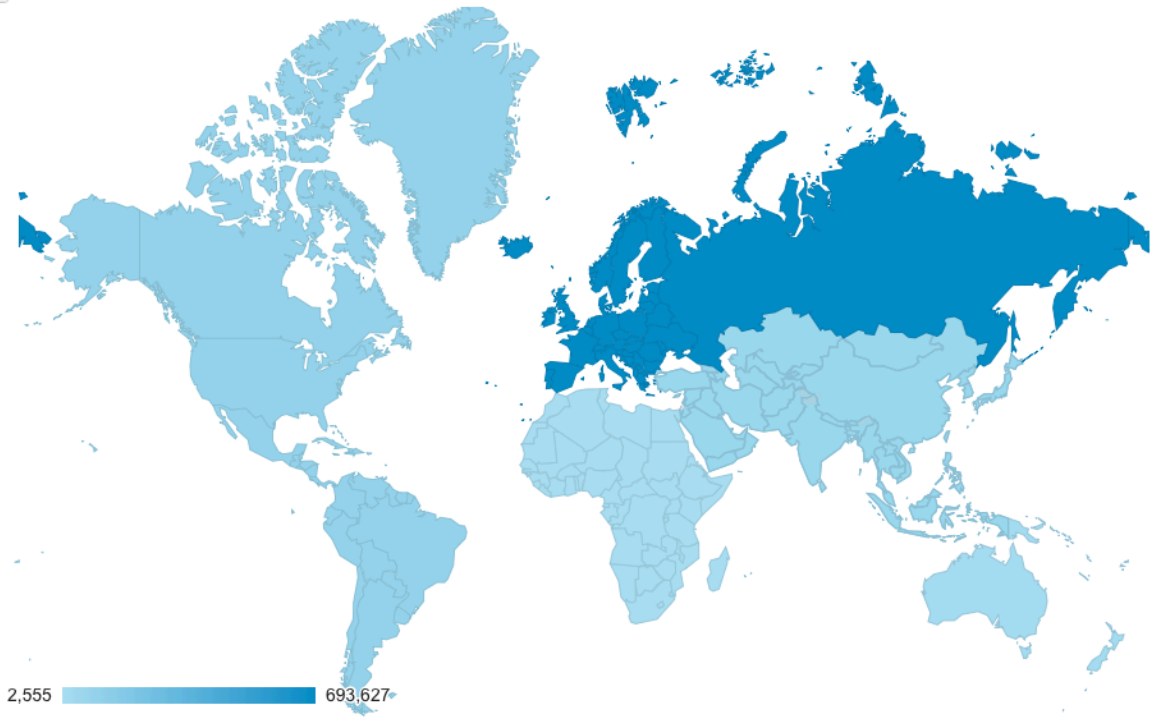
+ Add Segment

9 Sep 2016 - 15 Sep 2019

Map Overlay | Explorer

Summary | Site Usage | E-commerce

Users



Primary Dimension: Country | City | **Continent** | Sub Continent

Secondary dimension | advanced

Continent	Acquisition			Behaviour			Conversions	
	Users	New Users	Sessions	Bounce Rate	Pages/Session	Avg. Session Duration	Goal Conversion Rate	Goal Completions
	866,873	888,044	2,547,153	29.17%	3.21	00:05:11	0.00%	0

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EXISTING RISK FACTORS IN QRISK -2007

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Age

Deprivation

Family History CHD

Smoking

SBP & BMI

Cholesterol/HDL

Treated hypertension

Julia Hippisley-Cox et al. BMJ 2008:bmj

thebmj

EXISTING RISK FACTORS IN QRISK2 -2008

- Age
- Deprivation
- Family History CHD
- Smoking
- SBP & BMI
- Cholesterol/HDL
- Treated hypertension
- Atrial Fibrillation
- Dlabetes
- Rheumatoid arthritis
- Ethnicity
- ➢ CKD (stages4 & 5)

Julia Hippisley-Cox et al. BMJ 2008:bmj

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What's New in QRISK3 -2017

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8 new risk factors added

- **CKD 3-5**
- Migraine
- Corticosteroids
- SLE
- **Severe mental illness**
- **Atypical antipsychotics**
- **SBP variability**
- Erectile dysfunction

- All risk factors associated with increased CVD risk in other studies
- Adding to QRISK3 makes risk assessment more accurate
- Available at qrisk.org now
- In QOF
- in NHS Health Checks

Julia Hippisley-Cox et al. BMJ 2017;357:bmj.j2099

thebmj

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QRISK3 VALIDATION

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Fig 1 Funnel plots of discrimination performance (Harrell's C) across 328 practices.

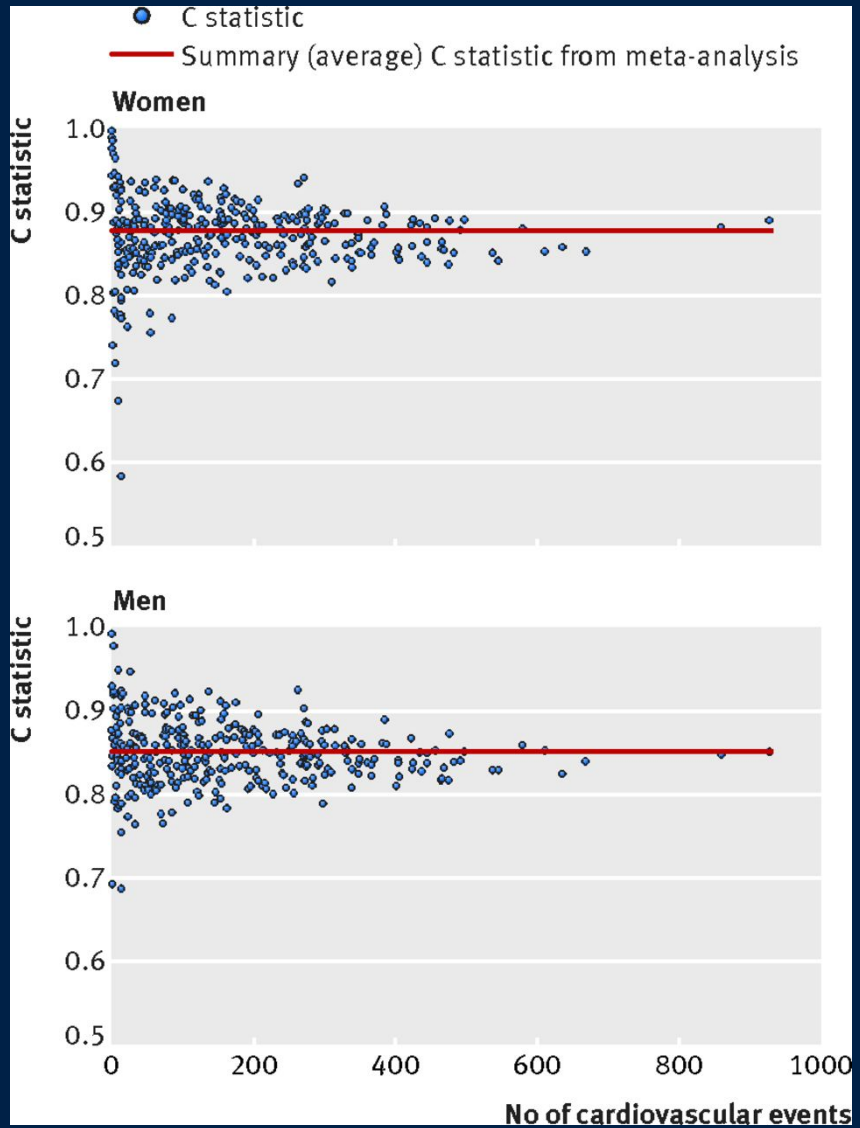


Table 1: Validation statistics showing performance of QRISK3 in Men and Women

	men	women
R2 variation	54.8%	59.6%
D statistic	2.26	2.48
Harrell's C	0.86	0.88

Julia Hippisley-Cox et al. BMJ 2017;357:bmj.j2099

thebmj

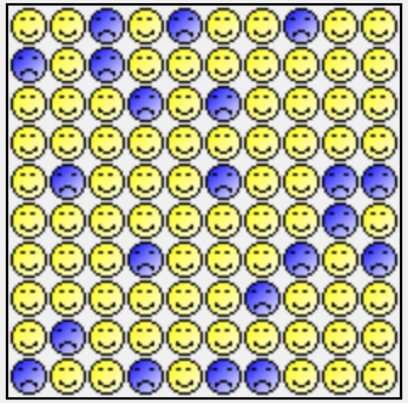
QRISK3 Web calculator https://qrisk.org/three/

Your results

Your risk of having a heart attack or stroke within the next 10 years is:

21.4%

In other words, in a crowd of 100 people with the same risk factors as you, 21 are likely to have a heart attack or stroke within the next 10 years.



Risk of
a heart attack or stroke

Your score has been calculated using estimated data, as some information was left blank.

Your body mass index was estimated as 27 kg/m^2.

- 55yr old heavy smoker
- FH CHD
- SMI
- Atypical antipsychotics
- QRISK2 score = 13.6%
- QRISK3 score = 21.4%

QRISK3 Web calculator https://qrisk.org/three/

How does your 10-year score compare?

Your score	
Your 10-year QRISK®3 score	21.4%
The score of a healthy person with the same age, sex, and ethnicity*	5.8%
Relative risk**	3.7
Your QRISK®3 Healthy Heart Age***	74

* This is the score of a healthy person of your age, sex and ethnic group, i.e. with no adverse clinical indicators and a cholesterol ratio of 4.0, a stable systolic blood pressure of 125, and BMI of 25.

** Your relative risk is your risk divided by the healthy person's risk.

*** Your QRISK®3 Healthy Heart Age is the age at which a healthy person of your sex and ethnicity has your 10-year QRISK®3 score.

- 55yr old heavy smoker
- FH CHD
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- Atypical antipsychotics
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Early diagnosis of cancer

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Early diagnosis of cancer: The problem

- 300,000 new cancers each year
- UK has relatively poor track record
- Partly due to late diagnosis with estimated 7,500+ lives lost annually
- Later diagnosis due to mixture of
  - late presentation by patient (lack awareness)
  - Late recognition by GP
  - Delays in secondary care
- Earlier diagnosis cancer improves chances of survival

What's the problem in General Practice?

- Many patients present with symptoms
- Most people with symptoms won't have cancer
- Need to decide which patients to investigate

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QCancer – what it needs to do

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1. Accurately predict individual risk of multiple cancers using on multiple risk & symptoms
2. Discriminate between patients
3. Guide decision on who to investigate + urgency.
4. Educational tool for sharing information with patient.

Methods – Development Algorithm

- Representative cohort from QResearch 2.5 million men & women aged 25-89 years
- Cancer outcome - all new diagnoses on GP record or linked record in 2 years
- Identify key risk factors
- Identify key symptoms
- Established methods to develop risk prediction algorithm
- Measure of absolute risk of any cancer + type

QCancer - overall risk & risk 12 types cancers

Lung	Pancreas	Renal	Ovary
Colorectal	Gastro	Testis	Cervix
Breast	Prostate	Blood	Uterus

- These accounts for 85% cancers
- Plan to extend to rarer cancers when sufficient data

Key Risk Factors in QCancer

Demographics life style

- Age
- Sex
- Smoking status
- Alcohol use
- Deprivation score
- Family history of cancer

Co-morbidities

- COPD
- Endometrial hyperplasia/polyp
- Chronic pancreatitis
- Type 2 diabetes
- Anaemia (HB < 11g/DL)
- Venous thromboembolism

Key Symptoms in Model

General

Loss of appetite
Unintentional weight loss
Indigestion +/- heart burn
Dysphagia
Abdominal pain or swelling
Constipation
Night sweats
Cough
Neck lump

Bleeding

Haemoptysis
Haematemesis
Haematuria
Rectal bleeding
Haematuria
Unexplained bruising

Women

Vaginal Bleeding
Breast lump
Breast pain
Nipple changes

Men

Genito-Urinary symptoms (men)
- Retention
- Nocturia
- Frequency
- Impotence
- Testicular lump

Validation of QCancer

- Essential to demonstrate the tools work and identify right people in an efficient manner
- Tested performance
  - ✓ separate sample of QResearch practices
  - ✓external dataset (Vision practices)
- Good at identifying those who do and don't have cancer
- Good at estimating level of risk
- Real world testing with 500+ GP practices by Macmillan and CRUK

Don't forget QCancer works out cancer risk NOT diagnosis

Using QCancer in practice

Standalone web calculator

www.qcancer.org

Integrated into clinical system

- Within consultation: GP with patients with symptoms
- Within consultation QOF style alert
- Run in batch mode to risk stratify populations

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Calculate risk

About you

Age (25-89): 64

UK postcode: leave blank if unknown

Postcode:

Clinical information

Smoking status: non-smoker

Alcohol status: non-drinker

Do you have...

a family history of gastrointestinal cancer? ☐
a family history of breast cancer? ☐
a family history of ovarian cancer? ☐
type 2 diabetes? ☐
chronic obstructive airways disease (COPD)? ☐
endometrial hyperplasia or polyp? ☐
chronic pancreatitis? ☐

Do you currently have...

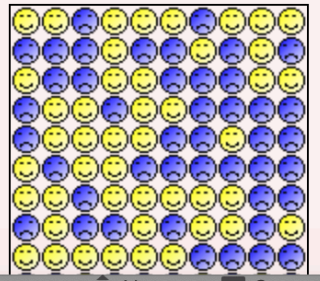
loss of appetite? ☑
unintentional weight loss? ☑
abdominal pain? ☑
abdominal swelling? ☑
difficulty swallowing? ☐
heartburn or indigestion: indigestion
rectal bleeding? ☐

Your risk of having one of the following cancers, as yet undiagnosed is:

Cancer	Type	Risk
No cancer		48.76%
Any cancer		51.24%
	ovarian	32.21%
	pancreatic	7.66%
	other	6.16%
	colorectal	2.72%
	gastro-oesophageal	1.45%
	lung	0.29%
	renal tract	0.26%
	blood	0.22%
	breast	0.21%
	uterine	0.04%
	cervical	0.02%

You have a 51.24% risk of having a cancer as yet undiagnosed, and correspondingly, a 48.76% chance that you are clear.

In other words, in a crowd of 100 people with the same risk factors as you, 51 are likely to have a cancer as yet undiagnosed and 49 will not, as shown by the chart below.



English (United States) Notes Comments

Woman age 64

- Weight loss
- Appetite loss
- Abdominal pain
- Abdominal swelling
- Indigestion

Overall risk cancer 51%

- Ovarian 32%
- Pancreatic 8%
- Colorectal 3%

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Using QCancer for Risk Stratification of future risk of cancer

BMJ 2019;367:l5558 doi: 10.1136/bmj.l5558 (Published 2 October 2019)

EDITORIALS

Check for updates

Personalised and risk based cancer screening

A radical shift that prioritises informed choice over maximising uptake

Philippe Autier *professor, population epidemiology*[1 2]

- Combine Risk Models with
  - Biomarkers
  - Devices
  - Imaging
  - Polygenic Risk Scores
- Redesign NHS Pathway to improve screening and early detection of disease

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QCancer 15 year risk stratification colorectal cancer

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ClinRisk

Welcome to the QCancer®(15yr,colorectal) risk calculator: http://qcancer.org/15yr/colorectal

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About you
- Age (25-84): 48
- Sex: Male / Female
- Ethnicity: White or not stated
- UK postcode: leave blank if unknown
  - Postcode:

Clinical information
- Smoking status: heavy smoker (20 or over)
- Alcohol status: none
- Do you have a family history of ...
  - gastro-intestinal cancer? ☑
- Women only: have you had any of these cancers?
  - breast cancer? ☐
  - uterine cancer? ☐
  - ovarian cancer? ☐
  - cervical cancer? ☐
- Men only: have you had any of these cancers?
  (These cancers did not pass our statistical test for significance for women.)
  - oral cancer? ☐
  - lung cancer? ☐
  - cancer of the blood? ☑
- Do you currently have...
  - Diabetes: type 2
  - ulcerative colitis? ☑
  - colonic polyps? ☐
- Leave blank if unknown
  - Body mass index
    - Height (cm):
    - Weight (kg):

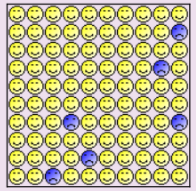
Calculate risk over 15 years. Calculate risk

Your results

Your risk of having colorectal cancer within the next 15 years is:

6.2%

In other words, in a crowd of 100 people with the same risk factors as you, 6 are likely to develop colorectal cancer within the next 15 years.



Risk of developing colorectal cancer

15 year Risk 6.2%

- Cohort study
- 5 million people
- Follow up to 15 years
- 32,000 cases Colorectal cancer

- Example shows man 48
- Heavy smoker
- Family history GI cancer
- Type 2 diabetes
- Ulcerative colitis
- Prior history blood cancer

Hippisley-Cox J & Coupland CA. BMJ Open 2015
http://dx.doi.org/10.1136/bmjopen-2015-007825

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Risk Stratified Colorectal Screening

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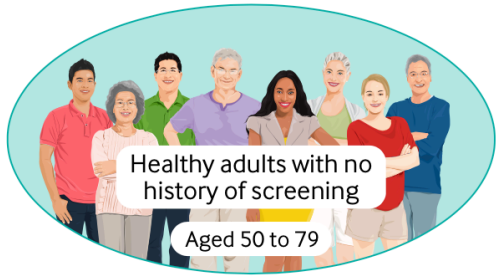
thebmj Research Education News & Views Campaigns Ar

Visual summary of recommendation

Population



Estimating risk

Understanding a person's risk of cancer can help to determine the benefits and harms of different screening tests for their individual situation.

We suggest using a tool such as the QCancer® calculator to estimate the risk of colorectal cancer for each person in the next 15 years. This calculates risk, based on:

Age | Sex | Ethnicity | BMI | Smoking status | Medical and family history

Link to QCancer® calculator qcancer.org/15yr/colorectal/

Practice » Rapid Recommendations

Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a clinical practice guideline

BMJ 2019 ; 367 doi: https://doi.org/10.1136/bmj.l5515 (Published 02 October 2019)
Cite this as: *BMJ* 2019;367:l5515

EDITORIALS

Check for updates

Personalised and risk based cancer screening

A radical shift that prioritises informed choice over maximising uptake

Philippe Autier *professor, population epidemiology*[1 2]

1. Persons priorities and characteristics prioritized
2. Clinicians focus on high risk people
3. Help optimize screening effectiveness
4. Reducing overdiagnosis in low risk

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Early Diagnosis Pancreatic Cancer - Biomarker

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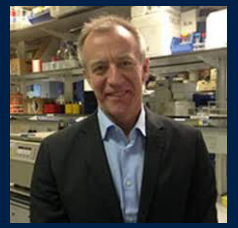

- The Early Diagnosis Research Alliance (EDRA) encompasses 4 complementary work packages to deliver early diagnosis for people with pancreatic cancer funded by Pancreatic Cancer UK.





Pancreatic Cancer UK

UCL

NHS National Institute for Health Research

UCLH Cancer Collaborative NHS

uclh NHS

Imperial College London

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QRESEARCH

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Thank you for listening & any questions