Sir Richard Doll Seminar

The Risk of Everything

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

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
GP Data
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- Prescriptions
- Diagnoses
- Lab investigations
- Clinical values
- Consultations
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Cancer registry
- Date diagnosis
- Type cancer
- Morphology
- Grade
- Stage
- Route to diagnosis
- Treatment
- Size

Mortality
- Date of death
- Up to 15 causes death
- ICD10 codes
• 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 45 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.

<table>
<thead>
<tr>
<th>Type of cancer (link goes to further information about the type of cancer)</th>
<th>QResearch Cases</th>
<th>percentage of all cancers on QResearch</th>
<th>total in England</th>
<th>percentage of all cancers in England</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin cancer (excluding melanoma)</td>
<td>251,124</td>
<td>22.4</td>
<td>2,050,847</td>
<td>20.5</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>112,401</td>
<td>10.0</td>
<td>1,015,410</td>
<td>10.1</td>
</tr>
<tr>
<td>Breast cancer (in situ)</td>
<td>12,743</td>
<td>1.1</td>
<td>103,081</td>
<td>1.1</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>93,496</td>
<td>8.3</td>
<td>786,900</td>
<td>7.9</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>92,712</td>
<td>8.3</td>
<td>901,024</td>
<td>9.0</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>90,156</td>
<td>8.0</td>
<td>821,153</td>
<td>8.2</td>
</tr>
<tr>
<td>Cervical cancer in situ</td>
<td>53,650</td>
<td>4.8</td>
<td>556,130</td>
<td>5.6</td>
</tr>
<tr>
<td>Malignant melanoma incl in situ</td>
<td>37,482</td>
<td>3.3</td>
<td>298,279</td>
<td>3.0</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>30,935</td>
<td>2.8</td>
<td>267,274</td>
<td>2.6</td>
</tr>
<tr>
<td>Non-Hodgkins Lymphoma</td>
<td>27,561</td>
<td>2.5</td>
<td>240,593</td>
<td>2.4</td>
</tr>
<tr>
<td>Bladder Cancer</td>
<td>26,163</td>
<td>2.3</td>
<td>256,078</td>
<td>2.6</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>20,804</td>
<td>1.9</td>
<td>185,481</td>
<td>1.9</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>19,868</td>
<td>1.8</td>
<td>179,395</td>
<td>1.8</td>
</tr>
<tr>
<td>Oesophageal cancer</td>
<td>18,813</td>
<td>1.7</td>
<td>170,025</td>
<td>1.7</td>
</tr>
<tr>
<td>Uterine cancer</td>
<td>18,026</td>
<td>1.6</td>
<td>156,033</td>
<td>1.6</td>
</tr>
<tr>
<td>Stomach (Gastric) cancer</td>
<td>18,020</td>
<td>1.6</td>
<td>188,543</td>
<td>1.9</td>
</tr>
<tr>
<td>Mouth (oral) cancer</td>
<td>17,832</td>
<td>1.6</td>
<td>154,348</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Representative Distribution of Patients across England

Overall, there are almost 33 million patient records on QResearch (version 43) between 1990 and 2018, from 1616 GP practices. This includes those who have died (2.15 million), 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.

<table>
<thead>
<tr>
<th>Region</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Midlands</td>
<td>1.54 million</td>
</tr>
<tr>
<td>East of England</td>
<td>1.67 million</td>
</tr>
<tr>
<td>London</td>
<td>9.23 million</td>
</tr>
<tr>
<td>North East</td>
<td>0.99 million</td>
</tr>
<tr>
<td>North West</td>
<td>5.07 million</td>
</tr>
<tr>
<td>South Central</td>
<td>4.55 million</td>
</tr>
<tr>
<td>South East</td>
<td>3.18 million</td>
</tr>
<tr>
<td>South West</td>
<td>3.49 million</td>
</tr>
<tr>
<td>West Midlands</td>
<td>3.47 million</td>
</tr>
<tr>
<td>Yorkshire and Humber</td>
<td>1.65 million</td>
</tr>
</tbody>
</table>

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...
Developing and Validating Risk Prediction tools
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
Risk of Multiple Outcomes

- 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
• 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
2007

Project Start

Build risk algorithm to estimate CVD risk
2007

**Project Start**
Build risk algorithm to estimate CVD risk

2007 NICE provisionally recommend
QRISK Timeline

2007

**Project Start**
Build risk algorithm to estimate CVD risk

**QRISK2**
Update algorithm following feedback

2007 NICE provisionally Recommend

2008 NICE Forbid
2007 NICE provisionally Recommend

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2009/10
Implement
Across health service

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- Project Start
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- NICE Allow

2014
- NICE mandate
- Guidelines updated
  - NICE recommended instead of Framingham

2007 NICE provisionally Recommend

2008 NICE Forbid
**QRISK Timeline**

**2007**
- **Project Start**
  - Build risk algorithm to estimate CVD risk

**2008**
- **QRISK**
  - Update algorithm following feedback

**2009/10**
- **QRISK2**
  - Update algorithm following feedback
- **Implement**
  - Across health service

**2010**
- **2010 NICE**
  - Allow

**2014**
- **2014 NICE mandate**

**2017**
- **QRISK3**
  - Updated with 8 extra risk factors
- **Guidelines updated**
  - NICE recommended instead of Framingham

**2019**
- **2019 NHS health checks**

**2007 NICE**
- provisionally Recommend

**2008 NICE**
- Forbid
Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study

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

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

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

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

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

Julia Hippisley-Cox, professor of clinical epidemiology and general practice
Carol Coupland, professor of medical statistics in primary care
Peter Brindle, evaluation and implementation theme lead, NIHR CLAHRC West
Cardiovascular disease: risk assessment and reduction, including lipid modification

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

HOW HEALTHY IS YOUR HEART?

The Heart Age Test:

- Tells you your heart age compared to your real age
- Explains why it's important to know your blood pressure and cholesterol numbers
- Gives advice on how to reduce your heart age

START

Full terms and conditions can be read here
EXISTING RISK FACTORS IN QRISK -2007

- Age
- SBP & BMI
- Cholesterol/HDL
- Treated hypertension
- Deprivation
- Family History CHD
- Smoking

Julia Hippisley-Cox et al. BMJ 2008:bmj
EXISTING RISK FACTORS IN QRISK2 - 2008

Age

SBP & BMI

Diabetes

Deprivation

Cholesterol/HDL

Rheumatoid arthritis

Family History CHD

Treated hypertension

Ethnicity

Smoking

Atrial Fibrillation

CKD (stages 4 & 5)

Julia Hippisley-Cox et al. BMJ 2008:bmj
What’s New in QRISK3 -2017

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
QRISK3 VALIDATION

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

<table>
<thead>
<tr>
<th></th>
<th>men</th>
<th>women</th>
</tr>
</thead>
<tbody>
<tr>
<td>R2 variation</td>
<td>54.8%</td>
<td>59.6%</td>
</tr>
<tr>
<td>D statistic</td>
<td>2.26</td>
<td>2.48</td>
</tr>
<tr>
<td>Harrell’s C</td>
<td>0.86</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Julia Hippisley-Cox et al. BMJ 2017;357:bmj.j2099
QRISK3 Web calculator https://qrisk.org/three/

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.

- 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

<table>
<thead>
<tr>
<th>Your 10-year QRISK® 3 score</th>
<th>21.4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>The score of a healthy person with the same age, sex, and ethnicity*</td>
<td>5.8%</td>
</tr>
<tr>
<td>Relative risk**</td>
<td>3.7</td>
</tr>
<tr>
<td>Your QRISK® 3 Healthy Heart Age***</td>
<td>74</td>
</tr>
</tbody>
</table>

* 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
- SMI
- Atypical antipsychotics
- QRISK2 score = 13.6%
- QRISK3 score = 21.4%
Early diagnosis of cancer
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
Many patients present with symptoms.

Most people with symptoms won’t have cancer.

Need to decide which patients to investigate.
QCancer – what it needs to do

1. Accurately predict individual risk of multiple cancers using on multiple risk & symptoms
2. Discriminate between patients
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
Q Cancer - 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**
- 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

www.qcancer.org
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

www.qcancer.org
Woman age 64
- Weight loss
- Appetite loss
- Abdominal pain
- Abdominal swelling
- Indigestion

Overall risk cancer 51%
- Ovarian 32%
- Pancreatic 8%
- Colorectal 3%

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.
Using QCancer for Risk Stratification of future risk of cancer

EDITORIALS

Personalised and risk based cancer screening
A radical shift that prioritises informed choice over maximising uptake

Philippe Autier professor, population epidemiology
• Combine Risk Models with
  – Biomarkers
  – Devices
  – Imaging
  – Polygenic Risk Scores
• Redesign NHS Pathway to improve screening and early detection of disease
Cancer 15 year risk stratification colorectal cancer

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

- Professors Coupland, Collins and Altman
- Prof Fitzgerald Cambridge
- Prof Steve Pereira UCL
- University of Nottingham
- University of Oxford
- EMIS Health
- GP practices
- Macmillan Cancer Research
- CRUK Oxford Centre
- Wellcome ISSF Fund
- ClinRisk Ltd (software)

This work uses data provided by patients and collected by the NHS as part of their care and support.

#datasaveslives
Thank you for listening & any questions