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Implementing polygenic scores for cardiovascular disease

into NHS Health Checks

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Contents

1. Introduction

1.1 Project rationale and scope

Recent advances in genetics have generated debates about the potential for polygenic score analysis to be used as a method of risk assessment, either by itself or, as part of new or existing risk assessment tools. This field has now reached a critical stage, with discussions moving towards potential implementation in the NHS. Following on from the PHG Foundation 2019 report 'Polygenic scores, risk and cardiovascular disease'[1], the purpose of this report is to consider the implementation and delivery of polygenic score analysis for cardiovascular disease (CVD) risk assessment as part of the NHS Health Check programme (also known as NHS Health Checks).

Our rationale for selecting this topic is that CVD is a common, serious condition with existing clinical risk assessment in place, and in the medium term (3-5 years) methods for incorporating polygenic score analysis into this process are likely to be available. The NHS Health Check programme is an existing population scale preventative risk assessment programme delivered across the NHS and local authorities in England. The scope, impact and effectiveness of this programme are currently being reviewed, and therefore an assessment of how polygenic scores could be incorporated is timely and relevant.

This report explores the changes needed to implement and deliver polygenic score analysis within existing practice, using the NHS Health Check programme as an exemplar for early implementation. The first half of this report describes the NHS Health Check programme and situates CVD risk assessment within this wider disease prevention programme. It describes how each aspect is delivered and what will need to change if polygenic scores are incorporated as a risk factor. The second half considers the short term implications of these changes, the impact that they may have on existing infrastructures, and the longer term potential for the use of polygenic score analysis for prevention of CVD.

1.2 Aims and objectives

The aim of this report is to consider the implications arising from the implementation and delivery of polygenic score analysis for cardiovascular disease in practice in the NHS, specifically in the context of the NHS Health Check programme. Underpinning our analysis is the assumption that a suitable, robust polygenic score model for implementation has been developed.

Specific objectives are to:

- describe the current clinical landscape for CVD risk assessment, focusing on the NHS Health Check programme

1 Moorthie S, Babb de Villiers C, Brigden T, et al. Polygenic scores, risk and cardiovascular disease. PHG Foundation. 2019

- consider what changes would be required to patient/healthcare professional interaction for polygenic scores to be implemented and delivered effectively as part of this multifactorial CVD risk assessment, within the NHS Health Check programme
- briefly highlight key operational and infrastructural changes that would be required should polygenic scores be incorporated into the NHS Health Check programme
- consider the longer term potential of incorporating polygenic scores into the NHS Health Check programme, and more broadly within healthcare
- outline conclusions and key considerations to help guide the implementation and delivery of polygenic scores in this context

1.3 Methodology

Our approach was to systematically analyse the current process of NHS Health Checks, exploring each stage in detail. This includes the identification of eligible patients; the invitation; written information and the decision to have an NHS Health Check; and the appointment and the return of results, which encompasses both immediate risk communication and subsequent risk management. For each aspect, we evaluated how delivery of the assessment will have to change if CVD polygenic scores are incorporated.

This process was informed by reviewing the literature to accurately describe each stage and by consulting with experts in the field. Eight in-depth interviews (telephone or in-person) with domain specific experts were also conducted, capturing expertise across CVD prevention, polygenic score development and utilisation, communication of genetic information, and behaviour change. These experts were selected to enhance our understanding of how information from polygenic scores can be used within the NHS Health Check more widely, how this might diverge from the current programme, the impact upon delivery, and what the resulting implications may be for healthcare professionals, policymakers and patients. A few broad questions were put to all interviewees, but other questions were developed to address and elicit individual expertise. A list of interviewees and their affiliations is included in Appendix 1.

1.4 Key assumptions

The report focuses on the use of a polygenic score model for CVD alongside non-genetic risk factors, to provide a combined risk estimate through the use of a risk tool. This approach seems closer to implementation than other methods such as the use of standalone polygenic scores for CVD and polygenic scores for underlying traits (such as blood pressure or cholesterol - known as 'partitioned' or 'partial' polygenic scores).[2]

2 Barroso I, McCarthy MI. The Genetic Basis of Metabolic Disease. Cell. 2019; 177(1):146-161

In this report we make the key assumption that there is sufficient evidence of clinical validity and utility to support the integration of polygenic scores into clinical / public health practice, including use across the major ethnic groups in the UK. However, there is widespread consensus that this is not yet the case, although there is increasing evidence that integrated risk prediction tools, incorporating polygenic scores, perform better than current clinical risk stratification tools, and offer greater opportunity for earlier intervention.[3] We make this assumption as there is an urgent need to address practical considerations around the delivery of this novel biomarker. These considerations will inform the development of the requisite expertise, processes, workforce, infrastructures and level of funding needed on a national scale in the near future.

As research involving polygenic risk scores is gaining pace, this report is intended as an exercise to consider the practical implications of embedding the use of this novel biomarker in advance of such evidence of clinical validity and utility becoming available. The report ends by providing conclusions regarding the delivery of polygenic score analysis for CVD as part of the NHS Health Check programme.[4]

3 Riveros-Mckay F, Weale ME, Moore R, et al. An integrated polygenic and clinical risk tool substantially enhances coronary artery disease prediction. Circulation: Genomic and Precision Medicine. 2021;14:e003304

4 This report focuses on provision of the NHS Health Check programme in England and excludes Wales and other devolved nations.

2. Genomics, polygenic scores and cardiovascular disease

2.1 Polygenic scores

Advances in genomics research are leading to improved understanding of the role that genetic factors (Box 1) play in the development of complex traits and common diseases. It is now well recognised that individual differences in predispositions to common disorders and complex traits, whether physiological or psychological, are influenced to a greater or lesser degree by genetic factors.[5] Polygenic scores (Boxes 2 and 3), are one way to estimate an individual's genetic susceptibility to a trait or disease, and are associated with many complex diseases and traits,[6,7,8] including CVD.[9] As scientific research continues, attention is now turning to whether and how this biomarker could be translated, incorporated and applied in healthcare systems.

The boxes below provide a short introduction to genomics and to polygenic scores.

Box 1. Genomics and genetic variation

DNA is the basic unit of heredity that is passed down from one generation to the next. DNA is made out of four chemical bases, labelled A, C, G and T. These bases are arranged in pairs in tightly coiled strings called chromosomes. The human genome contains around 12 billion bases or 6 billion base pairs, although the reference human genome comprises half this number (i.e. 6 billion bases or 3 billion base pairs): half of these are inherited in chromosomes from their mother, and half in chromosomes from their father.[10] The total set of DNA in a given human or other organism is called their genome. This is made up of non-coding DNA and genes, which are the coding sections of DNA that are translated into RNA and subsequently turned into proteins. There are estimated to be 20,000 genes in the human genome.

5 Price AL, Spencer CCA, Donnelly P. Progress and promise in understanding the genetic basis of common diseases. Proc. R. Soc. B. 2015; 282(1821)

6 Vassos E, Di Forti M, Coleman J, et al. An Examination of Polygenic Score Risk Prediction in Individuals With First-Episode Psychosis. Biol Psychiatry. 2017 Mar 15; 81(6): 470-7

7 McCarthy MI and Mahajan A. The value of genetic risk scores in precision medicine for diabetes. Expert Review of Precision Medicine and Drug Development. 2018; 3(5): 279-81

8 Seibert TM, Fan CC, Wang Y, et al. Polygenic hazard score to guide screening for aggressive prostate cancer: development and validation in large scale cohorts. BMJ. 2018 Jan 10; 360: j5757

9 Inouye M, Abraham G, Nelson CP et al. Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults: Implications for Primary Prevention. J Am Coll Cardiol. 2018 Oct 16; 72(16): 1883-93

10 National Research Council (US) Committee on Mapping and Sequencing the Human Genome. Mapping and sequencing the Human Genome. Washington (DC). National Academies Press (US)

Genetic variation

Around 99.9% of the bases in a human genome are identical in all humans. However, 0.1% of the genome varies between people. These variations occur for many reasons, mainly because, when DNA is copied and passed on from parent to offspring, there are invariably changes (or variations) that can occur.

Single nucleotide polymorphisms (SNPs)

Genetic variation as a result of changes to a single base, for example a change from an A to a C are referred to as single nucleotide variants. Such variants can either be common or rare in populations. Common single nucleotide variants are those that are present in at least 1% of the population. These are often referred to as single nucleotide polymorphisms or SNPs (pronounced 'snips').

Box 2. What is a polygenic score?

SNPs, disease risks and polygenic scores

In most cases, common SNPs either have no known impact on disease risk, or are only associated with complex traits and disorders by a tiny amount individually. However, when the effects of hundreds, thousands, tens of thousands or even millions of these small effect SNPs are added together, they can inform the risk of developing a disease or trait. Combining the information from these SNPs is known as a polygenic score (also referred to as 'polygenic risk score') for a particular trait or disorder. This score is normally distributed in a population, providing a spectrum of risk. For an individual, it may be informative to understand both an individual's score and where it lies along this normal distribution of risk.

Development of a polygenic score model

A polygenic score model is a mechanism to calculate the combined effect of SNPs across the genome. A polygenic score model is developed using data from Genome Wide Association Studies (GWAS) for a particular disease. These studies use SNP arrays to obtain genotype information from individuals with and without particular diseases. This data is analysed to identify SNPs that might be associated with specific traits and their effect size.

Different statistical approaches can be used in model development. All models need to be rigorously tested and validated to check their predictive capabilities. Once proven to do this reliably they can be used to calculate polygenic scores for individuals and inform estimates of their risk of developing particular diseases.

Box 3. Polygenic scores: useful terminology

The literature on polygenic scores uses the terms model, score, analysis and tool in a variety of ways.

Polygenic score: a number that provides information about a trait or condition based on a combination of common genetic variants (SNPs); the output of a polygenic score model.

Polygenic score model: the mechanism for calculating a polygenic score. There are different statistical approaches for the selection and weighting of relevant SNPs, each resulting in different models.

Polygenic score analysis: the process of applying a polygenic score model to genotype (SNPs) data through to obtaining and interpreting the output.

Risk tool: a mechanism for combining multiple risk factors to obtain a composite risk estimate for an individual for a given disease over a particular time period.

2.2 Description of polygenic scores for cardiovascular disease

Cardiovascular disease (CVD) has a significant genetic component, with heritability estimates for CVD conditions such as coronary artery disease (CAD) ranging from 50-60%.[11] For the vast majority of the population, the genetic component of CVD is polygenic, with many common variants contributing to risk. This has led to numerous efforts to develop polygenic score models for CVD, which can be used to predict disease risk.[12] This information has the potential to improve the accuracy of risk assessments for CVD.

CVD encompasses a broad group of conditions that affect the heart and circulatory system. Polygenic score models have been developed for specific subgroups of cardiovascular disease, such as CAD[13] and stroke,[14] or intermediate causes of cardiovascular disease such as atrial fibrillation[15] and hypertension.[16]

11 Wai X, Wiernek S, Evans JP, et al. Genetics of coronary artery disease and myocardial infarction. World J Cardiol. 2016; 8(1): 1-23

12 Moorthie S, Babb de Villiers C, Brigden T, et al. Polygenic scores, risk and cardiovascular disease. PHG Foundation. 2019

13 Aragam KG, Natarajan P. Polygenic Scores to Assess Atherosclerotic Cardiovascular Disease Risk. Circulation Research. 2020; 126(9): 1159-1177

14 Hachiya T, Hata J, Hirakawa Y, et al. Genome-Wide Polygenic Score and the Risk of Ischemic Stroke in a Prospective Cohort. Stroke. 2020; 51(3): 759-765

15 Muse ED, Wineinger NE, Spencer EG, et al. Validation of a genetic risk score for atrial fibrillation: A prospective multicenter cohort study. PLoS Med. 2018; 15(3): p.e1002525

16 Lukacs Krogager M, Skals RK, Appel EVR, et al. Hypertension genetic risk score is associated with burden of coronary heart disease among patients referred for coronary angiography. PLoS One. 2018; 13(12): p.e0208645

Predicting CVD risk can be done either through using a combination of different models developed for different subtypes or using a model that is generic across subtypes. Polygenic score models are also being developed for conditions associated with CVD, such as diabetes and obesity. The use of these CVD-related polygenic score models could potentially refine overall risk prediction of CVD; however, the focus in this report will be on implementation of polygenic score models directly predicting CVD.

There are currently 38 polygenic score models for CVD and related conditions registered in the PGS Catalog.[17] CAD, a sub-type of CVD, is one of the best-studied cardiac conditions and polygenic score model development is most advanced in this area, with 14 out of the 38 polygenic score models in the PGS Catalog predicting risk of developing CAD.[18] For this reason, much of the research on polygenic score model development focuses specifically on CAD rather than on the collective group of conditions comprising CVD. Nevertheless, models developed for CAD can also inform the prediction of risk of CVD more broadly because CAD is a key contributor to CVD. The number of SNPs included in CVD polygenic score models ranges from 27 to over 6.5 million. The additional improvement gained with increasing numbers of SNPs must be balanced against the cost of obtaining this data, as well as the additional gains in predictive ability each added SNP provides.[19]

When it comes to applying CVD polygenic score models in the clinic, the optimal number and specification of which SNPs to include is yet to be determined. The genetic complexity of the condition being investigated, the data sets used for the model development, and the model used to calculate the polygenic score, all impact the overall accuracy. As these factors vary for each polygenic score model developed, it can be hard to directly compare the performance of different models. Furthermore, the majority of polygenic score models have been developed in predominantly white European populations. This means they perform better in these populations than in populations of other ancestries. This issue with existing models is widely acknowledged and efforts are underway to develop new models and improve the generalisability of existing models.[20]

Studies suggest that polygenic scores for CAD can have similar predictive ability to some clinical risk factors, (e.g. high blood pressure, high cholesterol, tobacco use) and may account for some risk not covered by these risk factors. Combining polygenic scores with clinical risk factors could therefore allow better discrimination between those at high and low absolute risk for CAD.[21]

17 The Polygenic Score Catalog. Available from http://www.pgscatalog.org/ [Accessed 4 June 2021]

18 Lambert SA, Gil L, Jupp S, et al. The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation. Nat Genet 2021; 53: 420–425

19 Gladding PA, Legget M, Fatkin D, et al. Polygenic Risk Scores in Coronary Artery Disease and Atrial Fibrillation. Heart Lung Circ. 2020; 29(4): 634-640

20 Roberts MC, Khoury MJ, Mensah GA. Perspective: The Clinical Use of Polygenic Risk Scores: Race, Ethnicity, and Health Disparities. Ethnicity & disease. 2019; 29(3): 513-516

21 Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. Nat Rev Genet. 2018; 19(9): 581-590

The predictive ability and relevance of a polygenic score for an individual will also depend upon the time frame used in the model. Polygenic scores can be calculated and presented over a fixed time frame (e.g. 5 or 10 year risk) or over that person's lifetime (e.g. 80 years).[22] The optimal choice of time period depends heavily on context (see section 5.2.3).

2.3 Potential applications of polygenic scores

Information from polygenic scores could potentially be used in healthcare in multiple scenarios across screening, disease assessment, and management.[23] In this report, we focus on screening for the purposes of disease prevention, and more specifically, risk assessment to inform who should be targeted for interventions such as statin prescription or targeted surveillance and lifestyle advice.

2.3.1 Where could CVD polygenic score models inform risk assessment?

The performance of a polygenic score model in a research setting does not guarantee its performance in a clinical or health improvement context, nor its clinical utility. For a polygenic score model to be classed as having clinical utility, there must be evidence that the model meets a specific need, and that its use improves upon any current clinical pathways already in place. In the case of CVD risk prediction, this often means adding to the predictive ability of current risk factors, as well as improving health-related outcomes.

There is now considerable interest in the potential applications of polygenic scores as a mechanism to inform more targeted prevention and treatment. For example, the increasing feasibility and affordability of polygenic score analysis were highlighted in Professor Sir Mike Richards' review of adult screening programmes in England, as one important means by which screening will become more 'risk stratified' in the future.[24] Polygenic scores are also discussed in the National Genomics Healthcare Strategy, *Genome UK: The Future of Healthcare*, as a potentially useful tool for preventative efforts.[25] It is also anticipated that polygenic scores will be utilised in a major new UK health research programme, Our Future Health (see section 5.1).

Comparisons between the potential impacts of using different types and combinations of risk factors could be highly informative. Figure 1 below provides an illustration of how polygenic scores could be used in stratifying populations at risk of CAD.

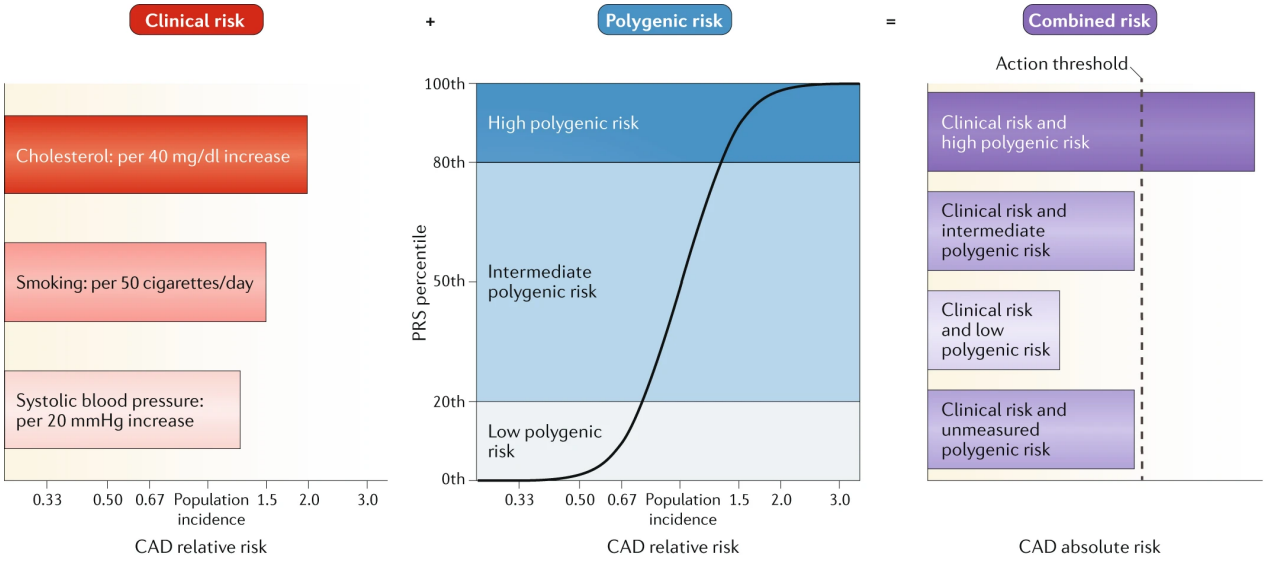
22 Inouye M, Abraham G, Nelson CP, et al. Genomic risk prediction of coronary artery disease in 480,000 adults: Implications for primary prevention. J Am Coll Cardiol. 2018; 72(16): pp. 1883-1893

23 Moorthie S, Babb de Villiers C, Brigden T, et al. Polygenic scores, risk and cardiovascular disease. PHG Foundation. 2019

24 Richards M. Report of the independent review of adult screening programmes in England. 2019. Available from: https://www.england.nhs.uk/wp-content/uploads/2019/02/report-of-the-independent-review-of-adult-screening-programme-in-england.pdf

25 Genome UK: The Future of Healthcare. Sept 2020. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/920378/Genome_UK_-_the_future_of_healthcare.pdf

Figure 1. Comparison of polygenic score for CAD compared to clinical risk factors.[26]



In the context of CVD, there are a number of purposes for which polygenic score models have been proposed to be useful. Some examples of these are outlined below.

Improving risk estimates to enable better stratification

Tools for determining an individual's risk of developing CVD on the basis of non-genetic risk factors have existed for many years (for example, QRISK®).[27] Composite scores combining polygenic scores and traditional risk factors could provide better predictive capability, allowing for better stratification and refinement of risk. This has implications for prescription of therapies or other interventions based on overall CVD risk levels, such as statins or targeted lifestyle advice, especially where individuals are reclassified from one intervention threshold to another.[28]

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26 Reprinted by permission from Springer Nature. Nature Reviews Genetics. (The personal and clinical utility of polygenic risk scores, Torkamani A, Wineinger NE, Topol EJ), [COPYRIGHT] (2018)

27 Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Derivation and validation of QRISK®, a new cardiovascular disease risk score for the United Kingdom. BMJ. 2007; 335: (7611)

28 Sun L, Pennells L, Kaptoge S, et al. Polygenic risk scores in cardiovascular risk prediction: A cohort study and modelling analyses. PLoS Med. 2021; 18(1): p. e1003498

Identify who could benefit the most from statin therapy

Research has been carried out to assess the clinical benefit of statin therapy in groups of individuals at different levels of CAD disease risk as determined by a polygenic score analysis.[29] This research demonstrated that even though individuals at all levels of risk benefited from statin use, people with higher polygenic risk had the larger relative and absolute reductions in disease risk following statin therapy compared to other risk groups.[30,31]

Earlier risk assessment to improve prevention of CVD

Genetic contributions to disease risk are measurable at birth and remain stable throughout the life-course. There is potential to identify individuals at high risk early in life before other clinical risk factors develop. On the basis of their polygenic score these individuals could then be targeted for interventions such as close monitoring, supporting lifestyle adaptation or potentially use of therapeutics. This is discussed further in section 5.2.2.

Target those with known genetic CVD risk factors

Using polygenic score analysis in those known to have rare genetic variants that are also risk factors for CVD could also be highly effective. For example, Khera et al's analysis of a cohort of patients hospitalised with early-onset myocardial infarction found that there were ten times the number of people with a high polygenic score than those with familial hypercholesterolemia (FH) mutations in this cohort, yet each conferred a similar increase in risk.[32] They note that whilst LDL cholesterol levels are an imperfect biomarker of the risks posed by FH, the risks conferred by high polygenic risk seem largely independent of traditional risk factors for CVD captured by existing risk tools. They conclude that this suggests that these risks are cumulative rather than duplicative, although the mechanistic underpinnings of the disease risk need more exploration.[33] In their recent review, Hadley et al also conclude that developing a screening and prevention framework for high polygenic risk in conjunction with population screening for FH could lead to greater improvements in population level prevention than current approaches.[34]

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29 Hadley TD, Agha A, Ballantyne C. How do we incorporate polygenic risk scores in cardiovascular disease risk assessment and management? Current Atherosclerosis Reports. 2021; 23:28

30 Natarajan P, Young R, Stitziel NO, et al. Polygenic Risk Score Identifies Subgroup With Higher Burden of Atherosclerosis and Greater Relative Benefit From Statin Therapy in the Primary Prevention Setting. Circulation. 2017; 135(22): 2091-2101

31 Mega JL, Stitziel NO, Smith JG, et al. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. Lancet. 2015; 385: 2264–71

32 Khera A. Whole-genome sequencing to characterize monogenic and polygenic contributions in patients hospitalized with early onset myocardial infarction. Circulation. 2019; 139: 1593–1602

33 Ibid.

34 Hadley TD, Agha A, Ballantyre C. How do we incorporate polygenic risk scores in cardiovascular disease risk assessment and management? Current Atherosclerosis Reports. 2021; 23:28

2.4 Summary

There is evidence in support of the use of polygenic scores to improve risk prediction for CVD. Polygenic score models for CVD appear to perform well in the cohorts in which they have been developed, and there are several ways in which they have been proposed to be useful in preventing CVD.

In this report we assume that polygenic score analysis has potential and could be used in the future, but recognise that many questions remain.[35,36] The next section of this report therefore focuses on how polygenic scores could be implemented in NHS Health Checks, once they have sufficiently demonstrated clinical validity and utility.

35 Moorthie S, Babb de Villiers C, Brigden T, et al. Polygenic scores, risk and cardiovascular disease. PHG Foundation. 2019

36 Moorthie S, Hall H, Janus J, et al. Polygenic scores and clinical utility. PHG Foundation. 2021

3. The NHS Health Check programme and cardiovascular disease

This section provides an overview of the NHS Health Check programme and situates CVD risk assessment within this context. It then goes on to appraise the value and potential implications of incorporating polygenic scores in the context of CVD risk assessment for NHS Health Checks.

3.1 The NHS Health Check programme

The NHS Health Check is a national programme which offers a free health check every 5 years to adults in England aged 40-74 years, not already diagnosed with a vascular condition. Local authorities became responsible for the risk assessment component of NHS Health Checks from April 2013, although the majority are delivered within primary care.[37] It aims to prevent CVD and associated conditions through the early assessment, awareness and management of risk factors known to interact with and affect the risk of developing non-communicable diseases, such as heart disease, diabetes and dementia. The NHS Health Check programme is a complex intervention with a range of outcomes (including follow-ups, onward referrals and prescriptions). In addition to case finding, it aims to engage with individuals to consider their modifiable risk factors.

Despite its objective to detect early signs of disease, and eligibility relying upon the absence of pre-existing disease, the NHS Health Check programme is not a formal screening programme overseen by the UK National Screening Committee.[38] Instead, it is classified as a 'national risk assessment, risk reduction and risk management'[39] programme. The activities of screening and prevention are sometimes difficult to distinguish, but this programme is clearly described as a prevention programme rather than formal screening for disease.

NHS Health Checks are offered by primary care physicians and practice nurses in a variety of settings, including general practices, pharmacies and community settings including mobile units or leisure centres.[40] Figure 2 describes how the NHS Health Check risk assessment process aligns with the

37 NHS England. Factsheet: Implementation of the NHS Health Check. Available from: https://www.england.nhs.uk/wp-content/uploads/2014/02/pm-fs-3-1.pdf

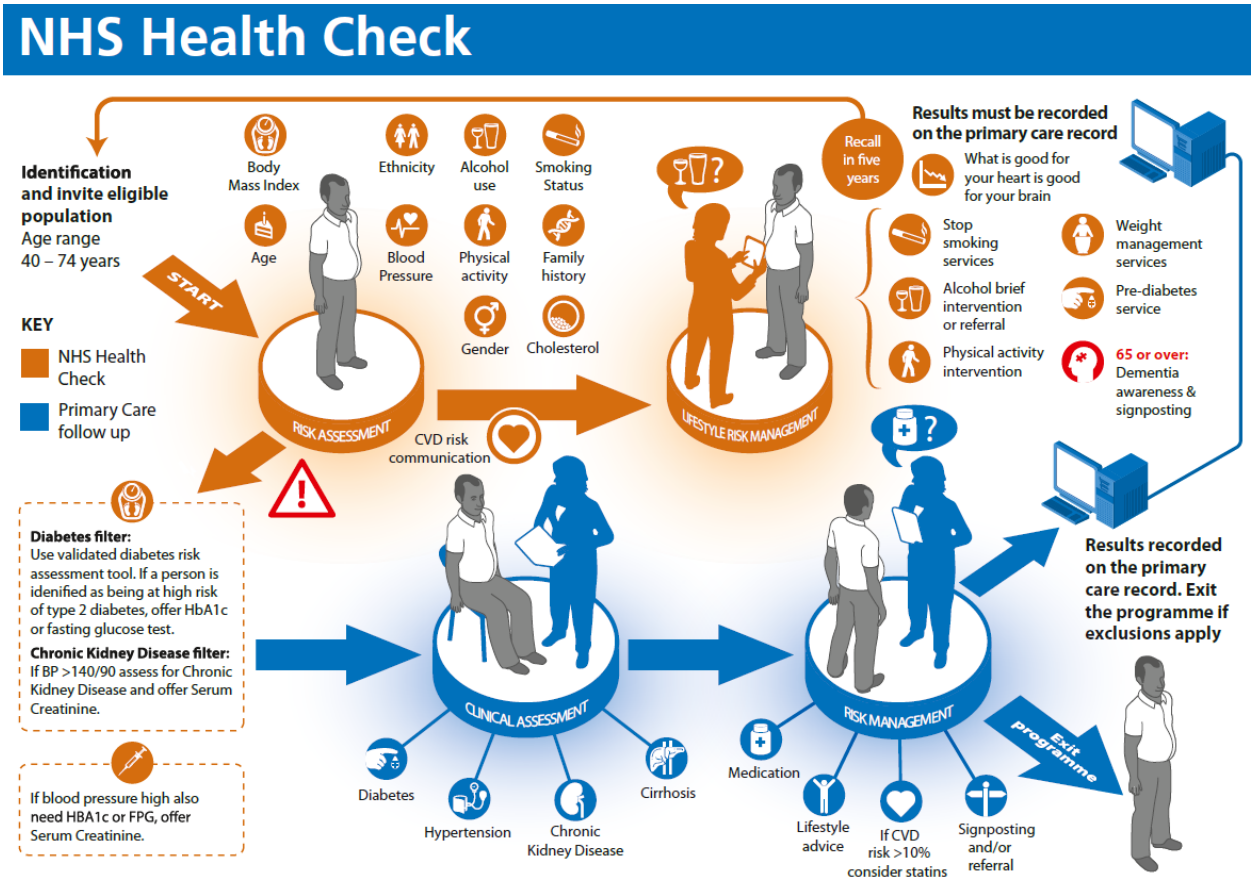
38 UK National Screening Committee. Guidance: Criteria for appraising the viability, effectiveness and appropriateness of a screening programme. Updated Oct 2015. Available from: https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme

39 NHS0040 [Public Health England] Appendix 1 para 3, cited in House of Commons Science and Technology Committee 'National Health Screening: Third Report of Session 2014-15'. October 2014. Available from: https://publications.parliament.uk/pa/cm201415/cmselect/cmsctech/244/244.pdf

40 NHS website. How do I get an NHS Health Check? Available from: https://www.nhs.uk/conditions/nhs-health-check/nhs-health-check/

clinical risk assessment process and subsequent clinical management for multiple conditions. Clinical management occurs within primary care. A clinical risk assessment process is triggered by clinical findings that might indicate undiagnosed diabetes, chronic kidney disease or hypertension. This contrasts with a formal screening programme overseen by the UK National Screening Committee which typically is limited to a single condition. Although Figure 2 shows the NHS Health Check risk assessment, management, and clinical assessment as discrete activities, in practice these may be carried out as part of an integrated risk assessment appointment.

Figure 2. NHS Health Check risk assessment and management[41]



41 Public Health England. NHS Health Check Best practice guidance for commissioners and providers. October 2019 (updated March 2020). Available from https://www.healthcheck.nhs.uk/commissioners-and-providers/national-guidance/

Box 4. The NHS Health Check Programme Review

An evidence based review of the NHS Health Check programme was announced in August 2019. This review is currently underway, and will explore how to improve the system, with a focus on offering personalised interventions based on factors such as age, socioeconomic factors and genetics.[42] This highlights the potential importance of genetics or genomics (including polygenic scores) in future risk assessments. These changes also reflect a shift away from blanket approaches to public health, towards more tailored, targeted services.

The government's NHS Health Check Review is also exploring:

- a special check-up for people approaching retirement age to help prevent or delay future care needs
- increasing the range of advice that NHS Health Checks can offer – for example, prevention of musculoskeletal problems or early action on hearing loss
- ways to increase the uptake of NHS Health Checks
- the digitisation of NHS Health Checks where appropriate

It is hoped that a review of the current programme could facilitate a 'more data led predictive system' which offers checks based on different risk factors.

3.2 Cardiovascular disease risk assessment

This report focuses on CVD risk assessment which is one aspect of the NHS Health Check programme. The NHS in England uses a variety of mechanisms to identify people at increased risk of CVD. This includes both opportunistic identification of those at high risk during routine visits (e.g. the Making Every Contact Count initiative which encourages making prevention central to all interactions between the public, and health and care workers)[43] and more formal mechanisms for identification of risk (e.g. NHS Health Checks). While the NHS Health Check programme does not focus exclusively on risk of developing CVD, and not all CVD risk assessments occur within its parameters, this intersection provides a framework for exploring the incorporation of polygenic scores and the implications that arise from their use.

42 Department of Health and Social Care. News story: Personalised health checks to be considered in new review. August 2019. Available from: https://www.gov.uk/government/news/personalised-health-checks-to-be-considered-in-new-review

43 National Institute for Health and Care Excellence. Making Every Contact Count: how NICE resources can support local priorities. Available from: https://stpsupport.nice.org.uk/mecc/index.html

3.2.1 Intended purpose of cardiovascular disease risk assessments

In England, NICE guidelines for CVD[44] recommend risk scoring as a way to prioritise and plan primary prevention interventions. CVD risk assessment is an integrated approach that assesses multiple risk factors to determine the absolute risk of experiencing a CVD event in a given period of time. It involves screening asymptomatic 'healthy' individuals to identify those estimated to be at 'high' risk of CVD. The intent is that high risk individuals, the group most likely to benefit from available interventions, can then be supported to engage in behavioural changes and/or receive targeted interventions that will lead to the prevention of a cardiac event or CVD-related traits. The overarching purpose is to increase the health, wellbeing and longevity of individuals in the general population via primary prevention.

Many CVD risk assessment tools are available[45] and used in primary care. The most commonly used is QRISK®3 which has been integrated into a number of electronic record management systems and is recommended both by NICE guidance[46] and NHS Health Check Best Practice Guidance.[47] QRISK®3, the latest iteration of a risk assessment tool developed by researchers at Oxford University, is a risk algorithm to calculate 10-year risk of developing CVD in men and women.[48] This timeline reflects NICE guidelines which require CVD risk assessment over a 10-year period.[49] An individual patient's absolute risk of having a heart attack in the next 10 years is assessed using a combination of risk factors such as alcohol use, physical activity, smoking status, weight, height, blood pressure, cholesterol and kidney function. In practice, QRISK®3 may also be used by GPs in an ad hoc manner, outside of the NHS Health Check programme as part of routine care.

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44 National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical Guideline [CG181]. 2014, updated 2016. Available from: https://www.nice.org.uk/guidance/cg181/chapter/1-recommendations

45 Many of these are outlined on pp 42-44 of our previous report: Moorthie et al. Polygenic scores, risk and cardiovascular disease. PHG Foundation. 2019

46 Currently the NICE guidance recommendation is "Use the QRISK®2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years." However, a surveillance review of the NICE guidance in January 2018 concluded that a partial update of the guidance is warranted to provide advice on the use of QRISK® 3.

47 Public Health England. NHS Health Check Best practice guidance for commissioners and providers. October 2019 (updated March 2020). Available from https://www.healthcheck.nhs.uk/commissioners-and-providers/national-guidance/

48 Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK®3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017; 357 :j2099

49 National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical Guideline [CG181]. 2014, updated 2016. Available from: https://www.nice.org.uk/guidance/cg181/chapter/1-recommendations

3.3 Summary

The NHS Health Check programme is a national risk assessment programme targeted at adults aged 40-74 years. It aims to spot early signs of disease (including CVD) through the combined assessment of multiple risk factors. It provides an opportunity for risk stratification and early preventative interventions, including the prescription of statins and targeted lifestyle interventions. It also provides a mechanism for early detection of several common complex diseases including heart disease and diabetes enabling stratification and improved clinical management.

Assessment of how polygenic score analysis for CVD can be integrated into the NHS Health Check programme is timely due to the policy push for the use of genomics in more stratified prevention strategies, and the ongoing NHS Health Check review (Box 4). The evolving landscape surrounding NHS Health Checks and their purpose as a risk assessment initiative makes them a useful exemplar for early implementation of polygenic scores.

4. Incorporating CVD polygenic score analysis into NHS Health Checks

This section addresses how cardiovascular disease (CVD) polygenic scores might be incorporated into the NHS Health Check programme at scale to improve the predictive accuracy of population wide CVD risk assessment, and ultimately to potentially reduce life-changing and fatal cardiac events. We examine the opportunities and barriers to implementation by (a) describing each component of the NHS Health Check pathway as currently carried out, and (b) evaluating how each component might need to change if a polygenic score were incorporated into the CVD risk assessment element of the NHS Health Check programme. For the purposes of this analysis, we make the assumption that the incorporation of a polygenic score improves the validity and predictive ability of the CVD risk assessment in this target population.

4.1 Identification of eligible patients

4.1.1 Current practice

In England, NHS Health Checks are offered to adults aged between 40 and 74 years, every five years, for the purposes of risk assessment, risk reduction and risk management of a range of common diseases. Eligible patients are generally identified by individual GP practices. Those already known to have heart disease or a related condition are excluded on the basis that these patients should already be receiving appropriate care.

Best practice guidance aims to ensure that there is uniformity and scale of provision across England whilst also allowing for local flexibility. This enables clinical commissioning groups (CCGs) and the practices within them to conduct NHS Health Checks according to their capacity and prioritise competing clinical demands. An underlying principle is 'proportionate universalism' to ensure that the scale and intensity of NHS Health Check delivery meets the degree of need.[50] This flexibility results in highly variable implementation nationwide. For example, some GP practices undertake a systematic search of their patient database every month, while other practices only do this once or twice a year. In addition, some GP practices only offer an NHS Health Check to patients who have been actively invited, while others use opportunistic approaches to invite patients, or enable patients to book an NHS Health Check on an ad hoc basis.

50 Public Health England. NHS Health Check Best practice guidance for commissioners and providers. October 2019 (updated March 2020). Available from https://www.healthcheck.nhs.uk/commissioners-and-providers/national-guidance/

If GP provision is assessed to be insufficient, or if there is a decision to target some patient populations at increased risk of disease, some councils commission services from private providers to supplement GP services. Some councils also offer alternative sites for Health Checks in the community setting to improve the range of choices available to patients; this is on the basis that GP practices offer limited accessibility outside working hours and some sections of the population (e.g. middle-aged men from lower socioeconomic groups) are less likely to take up Health Check invitations from GP practices.[51] Allowing some flexibility is therefore important so that programmes can be tailored to local factors.

4.1.2 What will change if polygenic scores are incorporated?

The process of determining eligible patients for NHS Health Checks would not need to change if a polygenic score was incorporated into the CVD risk assessment.[52]

However, one potential application of polygenic scores could be to inform the prioritisation of invitations within the eligible group. Although NHS Health Checks has always been an inclusive programme, the NICE guidelines for CVD risk assessment recommend that health care providers 'prioritise people on the basis of an estimate of their CVD risk before a full formal risk assessment.'[53] On this basis, polygenic score analysis could be carried out in advance of the Health Check appointment as part of this process to estimate CVD using risk factors already recorded in primary care electronic medical records. Work is underway to explore whether using polygenic scores alone or in combination with information already in the health record effectively prioritises patients for a formal assessment.

4.2 Invitation, informed choice and the decision to attend an NHS Health Check

4.2.1 Current practice

Most patients attend their NHS Health Check appointment in response to a written invitation from their GP, practice nurse or local authority. Most often, the GP or other healthcare professional/service sends out an invitation letter, and this is sometimes, but not always, accompanied by an information leaflet. Increasingly, GP practices invite patients via text message, or sometimes invite their patients to have an NHS Health Check verbally during pre-existing appointments for other clinical reasons. In some practices, patients can also request a health check if they are eligible and have not had one.

51 Graley CE, May KF, McCoy DC. Postcode Lotteries in Public Health - The NHS Health Checks Programme in North West London. BMC Public Health. 2011; 11: 738

52 This assumes NHS Health Checks would continue being offered only to adults between 40 and 74 years of age. There is, however, a debate to be had about whether CVD risk assessments such as QRISK®3 that incorporate polygenic scores would be more appropriately carried out at a younger age.

53 National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical Guideline [CG181]. 2014, updated 2016. Available from: https://www.nice.org.uk/guidance/cg181/chapter/1-recommendations

In addition to the invitation, patients can access information about NHS Health Checks via the NHS website. On the basis of this information, or without viewing it, patients make their decisions about whether or not to attend for an appointment. In primary care, as in other areas of healthcare, supporting *informed choice* (Box 5) is a central component of the person centred healthcare approach, and this applies to NHS Health Checks as much as other activities that healthcare professionals undertake. Therefore, in order for patients to make informed decisions about attending NHS Health Checks, these materials must be accurate and accessible.

Box 5. Informed choice

Informed choice is distinct from the legal concept of informed consent, the primary purpose of which is to protect patients against assault or battery in the form of unwanted medical interventions. The fundamental goal in enhancing patient choice is to enable patients to come to an autonomous decision which reflects their personal preferences. It might be difficult to reconcile measures to support informed choice with encouraging a specific choice to be made, for example to increase uptake of a screening test.

In some instances, informed choice about undergoing an NHS Health Check and the CVD risk assessment is supported through a verbal conversation between the GP or other healthcare professional and the patient.

Thus, the healthcare professional needs to be able to provide information to the patient, listen to them, and answer any questions they have.

4.2.2 What will change if polygenic scores are incorporated?

There would be no reason to change the invitation letters sent out by GP practices and local authorities if polygenic scores were incorporated into NHS Health Checks, given that these letters rarely mention the risk factors included in the CVD risk assessments.[54]

However, both the information leaflet accompanying the invitation letter, and the NHS website, would need revising to include information about polygenic scores. This is because both list risk factors included in the risk assessment. For example, the website section titled, “What happens at an NHS Health Check?” informs patients that there will be ‘questions, measurements and tests’. It states that the questions will include ‘whether any of your close relatives have had the illnesses being checked for’ (i.e. family history) and ethnicity, among other questions; and that the tests will include blood pressure, cholesterol and possibly also blood sugar levels.

54 This is the case provided that polygenic scores are not used to prioritise invitations, as described in section 4.1.2.

Changes to the information leaflet might include:

- that a blood or saliva sample will also be taken for a genetic test
- a generic explanation of what a polygenic score is
- how this contributes to the CVD risk assessment process used in NHS Health Check

Additions to online resources might include more details about the value added by using polygenic scores for CVD, and the implications of the results obtained e.g. that this informs the stratification of 'high' or 'low' risk and potential implications for ongoing treatment and management. Online resources might also be revised to address the implications of declining to provide a DNA sample for polygenic score calculations (e.g. that CVD risk assessment could still take place using other existing risk factors).

Given patients are currently provided with transparent information about the existing risk factors that are assessed, it is reasonable that there should be a similar level of transparency regarding the additional test to incorporate polygenic score analysis. This transparency requirement also applies to the instances where patients consult their healthcare professional in advance of attending a Health Check. In order to have an informed discussion, healthcare professionals would need an understanding of the risk factors involved (including this additional risk factor). This would require access to specific educational resources.

Health Education England (HEE) has established a Genomics Education Programme for the healthcare workforce, in collaboration with NHS England, higher education institutions and The Royal College of General Practitioners (amongst others). This programme consists of resources for healthcare professionals, spanning formal qualifications (months/years), long courses (weeks), short courses (hours), and factsheets, guides and videos. These resources focus on different aspects of genomics in healthcare to provide clear information on core genomics concepts and applied genomics, some of which are intended as clinical resources for specific audiences/roles and others aimed at NHS staff more broadly. Amending these resources to include discussion of polygenic score analysis could therefore be part of HEE's portfolio.

The findings from our literature reviews and from interviews suggest that in primary care, clinicians would need 'just-in-time' rather than 'just-in-case' educational resources on polygenic scores, e.g. brief online training and online resources, made available shortly before they are needed. However, the integration of polygenic scores into primary care might also present an opportunity to embed genomics education into medical training so that healthcare professionals are equipped with a basic understanding of genomics as it is mainstreamed.

Box 6. Public trust, and the impact of polygenic scores on uptake

The largest nationwide study of the NHS Health Check programme, using primary care data, found that checks were offered to over 9.5 million people during a 5-year cycle up to 2017, with 52% of people taking up the offer.[55] This is lower than the 75% that was anticipated when the programme was introduced. Quantitative studies have shown that uptake is generally higher in older people, women, those with hypertension and raised cholesterol, non-smokers and patients registered with smaller practices.[56,57,58] There are many reasons why individuals may opt not to have a Health Check. These include misunderstanding the purpose of the check, lack of interest or 'not wanting to know', and time constraints or competing priorities.[59] The success and effectiveness of the NHS Health Check programme also relies upon public trust, which further influences uptake.

It is unclear whether incorporating polygenic score analysis will act as a barrier, act as an incentive, or have no discernible impact on uptake of NHS Health Checks. There is no evidence around the impacts of polygenic scores on the uptake of risk assessments more generally but some research has been conducted looking at public opinion and attitudes to genetic testing more generally. This research suggests that whilst public opinion on genetics is generally favourable, it is heavily dependent on the type of genetic application and the purpose it is used for.

Overall, technologies that lead to the detection and treatment of disease are considered valuable.[60] One study found that 92% of participants indicated that they agreed or strongly agreed with the use of DNA testing for early detection of diseases.[61]

55 Patel R, Barnard S, Thompson K, et al. Evaluation of the uptake and delivery of the NHS Health Check programme in England, using primary care data from 9.5 million people: a cross-sectional study. BMJ Open. 2020; 10: e042963

56 Dalton AR, Bottle A, Okoro C, et al. Uptake of the NHS Health Checks programme in a deprived, culturally diverse setting: cross-sectional study. J Public Health (Oxf). 2011; 33(3):422–429

57 Robson J, Dostal I, Sheikh A, et al. The NHS Health Check in England: an evaluation of the first 4 years. BMJ Open. 2016; 6:e008840

58 Martin A, Saunders CL, Harte E, et al. Delivery and impact of the NHS Health Check in the first 8 years: a systematic review. British Journal of General Practice. 2018; 68 (672): e449-e45

59 Harte E, MacLure C, Martin A, et al. Reasons why people do not attend NHS Health Checks: a systematic review and qualitative synthesis. British Journal of General Practice. 2018; 68 (666): e28-e35

60 Henneman L, Vermeulen E, van El CG, et al. Public attitudes towards genetic testing revisited: comparing opinions between 2002 and 2010. Eur J Hum Genet. 2013;21(8):793-799

61 Haga SB, Barry WT, Mills R, et al. Public knowledge of and attitudes toward genetics and genetic testing. Genet Test Mol Biomarkers. 2013;17(4):327-335

However, the authors of this study acknowledged that these positive attitudes may also be attributed to the participants' interest/willingness to participate in a study about genetic testing and therefore, may not be representative of the general population. On the other hand, there is also evidence to suggest that some individuals are wary of undergoing genetic testing, preferring to forgo the potential advantages of receiving polygenic information for fear that insurers[62] or commercial companies might have access to this data down the line.[63]

Evidence on public attitudes towards incorporating a genetic component into NHS Health Check is important in ascertaining whether this would encourage or discourage uptake, and if the latter then what mitigations could be put in place. One possible mitigation could be that the inclusion of a polygenic score is based on the preferences of the individual. Although assessing the full set of risk factors is recommended, QRISK® can compute a risk result in the absence of one or more risk factors, for example if a patient has not had a cholesterol test.

Similarly, providing the option of having a Health Check without the polygenic score component would ensure continued Health Check provision to those who objected to this component or did not have DNA available for other reasons. Reasons could include objections on the basis of the sensitive nature of genomic information and related concerns around privacy and secondary uses of data. Indeed, equal access to Health Checks may become even more important, as 'the routine clinical use of PRS [polygenic risk scores] has the potential to exacerbate health disparities even if equal predictive power is obtained across different ancestry groups, for the all too familiar structural reasons that cause those disparities in the first place, including lack of access to care.'[64]

4.3 The NHS Health Check appointment

4.3.1 Current practice

The NHS Health Check is a 20-30 minute appointment, within which the healthcare professional, often a nurse or healthcare assistant, asks questions about the individual's lifestyle and family history, measures their height and weight, takes their blood pressure, draws blood, and returns available results. The process of gathering this information can take several forms. In GP practices that use point of care testing (POCT), all measurements can be taken and results returned in a single appointment.[65] In other cases, blood tests are taken separately (within a GP practice, or phlebotomy service), sent to a laboratory for analysis, and the other risk results are then collected and combined and fed back in a separate appointment. The CVD risk assessment result is sometimes returned in the

62 Lewis A, Green R. Polygenic risk scores in the clinic: new perspectives needed on familiar ethical issues. Genome Medicine. 2021; 13:14

63 Wellcome Trust. One way mirror: public attitudes to commercial access to health data. 2016. Available from: https://wellcome.org/sites/default/files/public-attitudes-to-commercial-access-to-health-data-wellcome-mar16.pdf

64 Lewis A, Green R. Polygenic risk scores in the clinic: new perspectives needed on familiar ethical issues. Genome Medicine. 2021; 13:14

65 El-Osta A, Woringer M, Pizzo E, et al. Does use of point-of-care testing improve cost-effectiveness of the NHS Health Check programme in the primary care setting? A cost-minimisation analysis. BMJ Open. 2017;7:e015494

appointment, or alternatively those who are low risk (with less than 10% risk of developing CVD in the next 10 years) are given their results in a letter or over the phone, as they do not need a face-to-face discussion about risk management and reduction. Therefore, the NHS Health Check can be spread over one or two appointments, and results are sometimes, but not always, delivered in person or via an e-consultation. NHS Health Checks often take place in GP surgeries, but can also occur in local pharmacies or even local libraries or leisure centres. In some areas, NHS Health Checks are offered from mobile units to passers-by and in workplaces.

This variability in practice reflects the fact that although there are legislative requirements[66] for provision of the core part of the Health Check, the NHS Health Check best practice guidance emphasises flexibility to enable local decisions on a wide range of factors. This includes how the assessments are provided; for example, who delivers the check, the use of POCT or venous blood samples, the integration of digital components or completion of some parts of the Check in advance.[67]

4.3.2 What will change if polygenic scores are incorporated?

In order to calculate an individual's polygenic score, five things need to happen (assuming that the genetic data is not already available): (1) a biological sample (such as blood or saliva) is taken; (2) DNA is extracted from the biological sample; (3) the DNA is then genotyped using a SNP array or 'SNP chip' (or alternatively genome sequencing); (4) the information from the relevant SNPs are selected and combined and analysed using a risk algorithm (polygenic score model) to produce a single score for the individual; (5) this score is then integrated into a risk assessment process (such as QRISK®3) which takes account of other relevant risk factors.

Operational issues relating to genotyping and analysis

The extraction of DNA from a biological sample, the provision of a SNP array to generate a genotype, and the calculation of a polygenic score which is then reported to a healthcare provider will require staff/resources and either the amendment of existing pathways or the creation of new ones. It is possible that existing pathways could be adapted to incorporate the additional steps of obtaining a blood or saliva sample for DNA extraction, and that this additional sample could be collected at the same time as other samples. This testing could be integrated into current NHS laboratory genetic testing facilities. Although POCT is possible for many of the existing risk factors used in the risk assessment (e.g. cholesterol and blood sugar), their use is non-uniform within NHS Health Checks.[68] POCT for the genotyping of variants is currently highly speculative due to its technical complexity, and is unlikely to be available in the short to medium term.

66 For example, The Local Authorities (Public Health Functions and Entry to Premises by Local Healthwatch Representatives) Regulations 2013 S.I. 2013/351 sets out who is eligible, what tests and measures are included in the assessment, and ensures that specific information and data are recorded during a check.

67 Public Health England. NHS Health Check Best practice guidance for commissioners and providers. October 2019 (updated March 2020). Available from https://www.healthcheck.nhs.uk/commissioners-and-providers/national-guidance/

68 El-Osta A, Woringer M, Pizzo E, et al. Does use of point-of-care testing improve cost-effectiveness of the NHS Health Check programme in the primary care setting? A cost-minimisation analysis. BMJ Open 2017;7:e015494

If genotyping were to be implemented at scale using current NHS genetic laboratories, this would have an impact on current service provision. Alternatively, commercial providers could deliver polygenic score genotyping services, including analysis, interpretation and reporting on a population wide basis from blood or saliva samples.[69] They could provide the requisite sample collection kits, processing, analysis and interpretation to deliver a variety of polygenic scores back to healthcare providers. Companies such as Genomics PLC work with health providers to offer a data analysis service in the UK for polygenic risk assessments of individuals or populations.[70]

Irrespective of the pathways adopted, pilots of polygenic scores will be needed to test and validate the proposed genotyping tests and analyses to be used in practice, to ensure that these components (processes, products, platforms and services) perform as expected and at scale for the population being tested.

Provision of the result to the NHS Health Check provider

In order to inform clinical decision making, a polygenic score would need to be generated for each patient in a timely manner. If the polygenic score is retained in the patient's electronic medical notes, it could be used as an ongoing resource to inform future CVD risk assessments. This is assuming that there is little change in the method employed to calculate the polygenic score over time.

Alternatively, if the genotyping data is retained and easily accessible, as methods progress, these could be applied to existing raw data to calculate a polygenic score with the latest algorithm. In this way, generating a polygenic score might be more cost-effective if regarded as having continuing utility over three decades of assessment (assuming the patient has assessments from age 40 - 74).

4.4 Return of results

The process of returning results to patients is the culmination of a series of steps. These include the healthcare professional or test provider: receiving and processing the relevant test results or scores; entering these results into a CVD risk calculator tool; discussing the composite score (and possibly specific component scores) with the patient; and finally making a decision with the patient about whether any action should be taken in response to that information.

It will be important to consider the impact that polygenic scores might have on this process and whether incorporating genetic information presents additional challenges. In our analysis, we separate out the presentation of risk to the healthcare professional, the communication of risk to the patient, and the subsequent shared decision-making about risk management into three discrete steps, although in reality, these are interlinked.

69 Saliva samples may be more likely to be taken as they are stable over days at a wide range of temperatures, whereas blood samples require timely transport.

70 Genomics PLC. 'For Health Systems'. Accessed 7 April 21. Available from: https://www.genomicsplc.com/precision-health/health-systems/

4.4.1 Presentation of risk to the healthcare professional

Before risk results are communicated to the patient, the results for the individual risk factors/traits and composite risk scores are presented to the healthcare professional. This is the first stage in the return of results process.

Current practice

The overall risk score for CVD is the result of a combination of individual risk factor results, entered into a risk prediction model. Some of these risk factors, or traits, are binary (e.g. do you have a family history?) whilst others can be 'normal' or 'high' or 'low'. These are often presented as a number (e.g. age, height, weight, and biomarkers such as blood pressure and total cholesterol levels). In each of these instances, guidelines that establish clinical thresholds are in place to indicate to healthcare professionals where the individual is on the scale of risk, and guide them towards appropriate interventions. This does not mean that, following a reading above this threshold, an intervention is always appropriate, but may indicate to the healthcare professional that they should consider its appropriateness, taking into account the totality of relevant information.

Once the healthcare professional has the information needed to calculate the patient's disease risk, the results/scores are then entered into the medical records and used to automatically populate the CVD risk calculation tool, most commonly QRISK®.[71] QRISK®3 uses a greater range of parameters than previous iterations of the risk calculator.[72]

The user interface for QRISK®2 and QRISK®3 varies between different GP systems. An example of one of these user interfaces is shown in Figure 3 (R) below. Here, QRISK®2 includes a single web page on which the patient's information/risk factor information is entered on the top half of the page, and a panel presenting the subsequent risk assessment result numerically is shown on the bottom half of the page.

An example of the web-based version of this tool is shown in Figure 3 (L): in this version, the data is entered on the left panel, and the right panel shows the result verbally, numerically and also graphically.

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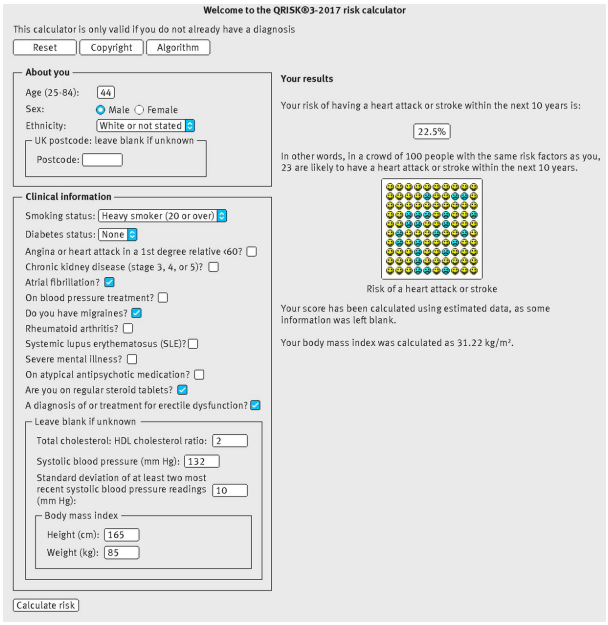
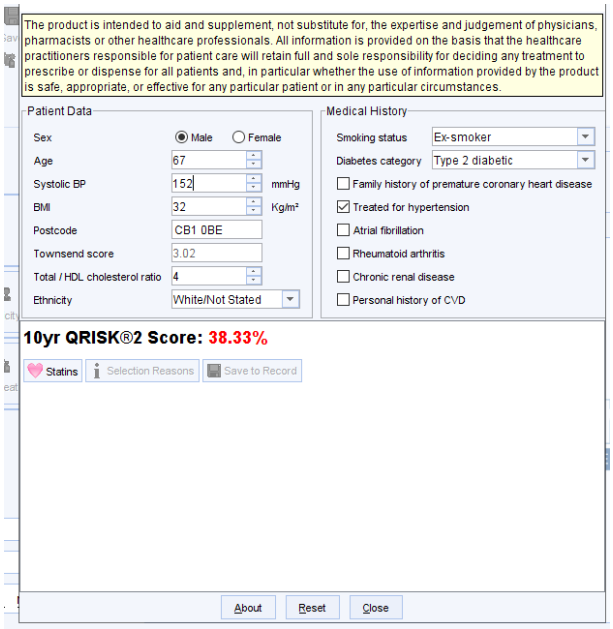
71 Currently the NICE guidance recommendation is 'Use the QRISK®2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years.' However, a surveillance review of the NICE guidance in January 2018 concluded that a partial update of the guidance is warranted to provide advice on the use of QRISK®3.

72 A full list of parameters can be found at https://www.qrisk.org/three/index.php [information page of QRISK®3 calculator]

Figure 3: Screenshot of a CVD risk calculator: QRISK®3 web based tool (L) and QRISK®2 using SystmOne (R)





Combined risk scores can be calculated during the appointment by the healthcare professional in front of the patient, and therefore need to be interpreted quickly and accurately by the healthcare professional.

As part of current NHS Health Check programme standards, there is a requirement that GP providers or alternative service providers produce evidence that all prescribed health indicators (as outlined in the best practice guidance) have been assessed, and that a record is made of the name of the healthcare professional involved, the NHS Health Check having been completed and date of completion.[73]

What will change if polygenic scores are incorporated?

As with the other risk factors, the polygenic score will need to be communicated to and understood by the healthcare professional prior to it being incorporated into the CVD risk calculator.

The process of returning a polygenic score result to the GP raises a series of infrastructural considerations that need to be addressed in order to avoid creating a bottleneck. These include considerations regarding where the sample is sent for analysis and who calculates the score. An additional practical consideration is how this genetic result will be returned and in what form (e.g. a risk score, or data requiring further interpretation).

73 Public Health England. NHS Health Check programme standards: a framework for quality improvement. July 2020. Available from: https://www.healthcheck.nhs.uk/commissioners-and-providers/national-guidance/

Launching a dialogue with healthcare professionals involved in delivering NHS Health Checks to understand what information they want returned and how they want it presented to them would be useful to establish their preferences and prompt early co-design and engagement with these issues.

Once this genetic result is fed back to the clinician, it needs to be incorporated into the CVD risk calculator. This is consistent with the ongoing evaluation and adaptation of risk tools which are regularly updated in line with emerging evidence (e.g. the progression from QRISK®2 to QRISK®3) to include newly discovered and re-evaluated risk factors.

The addition of polygenic scores into the CVD risk calculator would need to be evaluated and tested within this risk prediction model to ensure that this additional data is accurately embedded within the risk calculation, and that this takes account of any updated epidemiological information, such as the prevalence and incidence of CVD within different populations. This evidence must be established before implementing in clinical care at a national level.

In terms of the user interface, the QRISK®3 risk calculator would need to have an additional box on the data entry panel of the web page: this is where the results of the patient's polygenic score would be entered, either manually, or more often automatically from electronic health records.

The software embedded within the electronic health record would also need to be updated to enable it to impute a missing polygenic score (especially if individuals have the option to decline the genetic component of the assessment). The panel showing the patient's CVD risk result could remain as it is: it would still be appropriate to describe the overarching result (e.g. '30%' or '30 out of 100 people like you…') to the patient in words, percentages, proportions, and using an icon array graphic.

4.4.2 Risk communication to the patient

Developing effective communication strategies about polygenic scores can build on existing evidence about what constitutes 'good' risk communication in other contexts and for other risk factors. There is extensive research on risk communication highlighting its central role in patient care.[74]

'Good' risk communication depends on purpose and context. The quality of risk communication cannot be assessed unless the objectives are clear. Outcome measures used in studies of risk communication vary, and can include audiences' comprehension, their liking of the material, feelings aroused, attitudes regarding threats, intentions for the future, and (rarely) actual changes in behaviour.[75]

Within the context of the NHS Health Check programme, there is some ambiguity around the goals of risk communication as some literature emphasises 'informing' and others 'persuading'. As a public health prevention initiative, the goals of risk communication mirror the aims of the programme: to inform the patient of their risk in such a way that they leave the consultation with the knowledge and intention to engage in health-protective behaviours that reduce CVD risk.

74 Spiegelhalter D. Risk and Uncertainty Communication. Annual Review of Statistics and Its Application. 2017;4(1):31-60

75 Ibid.

In practice, this balance between 'informing' and 'persuading' will be different for each patient, and will be at the clinician's discretion, taking account of other relevant professional guidance.[76] The narrative in clinical discourse is also moving away from persuasion towards 'enablement' and 'empowerment'.

Therefore, in practice healthcare professionals may aim to communicate risk so as to help support the patient to understand the implications and impact of their result, and provide a foundation of understanding from which they can assess which risk management decisions are right for them. Done well, risk communication should 'turn data into something more meaningful, relevant and useful for individual patients.'[77]

Current practice

Risk communication is an essential part of shared decision making and supporting evidence-based patient choice. The NHS Health Check programme standards[78] for commissioners and providers state that staff responsible for communicating individual disease risk information to patients should be trained to 'communicate risk in everyday, jargon-free language so that individuals understand their level of risk.' The guidance also states that face-to-face conversations between professionals and patients should be supported by 'individualised written information, including results.'

However, clinician-patient interactions are complex and communicating risk is challenging. A review of 70 risk scoring methods concluded that there is no single 'correct' approach to risk communication; rather, this will depend on an individual's preferences and understanding, which in turn may differ by educational status, numeracy, and personality traits such as optimism.[79] Therefore, using a combination of strategies for communicating risk may be most effective, including using descriptive terms (low, medium, high etc.), numerical data and visual aids/graphics.

Absolute and relative risk

NHS Health Checks website materials directed at patients state that healthcare professionals may provide estimated personal CVD risk of developing a heart or circulation problem (such as heart disease, stroke, type 2 diabetes or kidney disease) as follows:

- low - the patient has less than a 10% chance of a heart or circulation problem in the next 10 years

76 General Medical Council. Good Medical Practice. March 2013 (updated April 2019). Available at https://www.gmc-uk.org/-/media/documents/good-medical-practice---english-20200128_pdf-51527435.pdf

77 Naik G, Ahmed H, Edwards AG. Communicating risk to patients and the public. Br J Gen Pract. 2012;62(597):213-216

78 Public Health England. NHS Health Check programme standards: a framework for quality improvement. July 2020. Available from: https://www.healthcheck.nhs.uk/commissioners-and-providers/national-guidance/

79 Beswick A, Brindle P, Fahey T, et al. A Systematic Review of Risk Scoring Methods and Clinical Decision Aids Used in the Primary Prevention of Coronary Heart Disease (Supplement) [Internet]. London: Royal College of General Practitioners (UK); 2008. (NICE Clinical Guidelines, No. 67S.)

- moderate - the patient has a 10% to 20% chance of a heart or circulation problem in the next 10 years
- high - the patient has more than a 20% chance of a heart or circulation problem in the next 10 years[80,81]

This strategy involves providing the patient with their absolute risk (i.e. the risks of developing cardiovascular disease over a ten year time period), which can be misleading on its own. Additional context can be provided through giving the patient their relative risk, which lets patients know how their personal risk is different to that of the general population e.g. 'the risk of you developing CVD in the next 10 years is about 18%' can only be interpreted when given more information about the population average. Like absolute risk, relative risk should not be disclosed on its own as it can exaggerate the perception of difference, particularly when absolute risks are very small.[82]

Using words alone is generally discouraged (e.g. 'high risk' and 'low risk') as this reduces trust, and can lead to lower accuracy and satisfaction, although these can be used alongside graphics[83] and numerical risks. This is because verbal descriptors are often elastic concepts with a high tendency to be misinterpreted.[84]

Numerical risk

Numerical risk can be given in different formats, which in turn can affect the risk perception of the patient. The most common options are percentages (e.g. 20%) and frequency (e.g. 20 in 100). It is unclear which helps people the most, but it is clear that everyone – regardless of education level - can get easily confused between them (e.g. mistaking 20% for 1 in 20).[85]

A study conducted by Gigerenzer et al showed that only 25% of the general population could correctly identify 1 in 1000 as being the equivalent of 0.1%.[86] It is also important to note that people respond differently to the same number expressed in different ways (with '20 out of 100' perceived to be higher than 20%, for example).[87]

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80 NHS website. 'Your NHS Health Check results and action plan'. https://www.nhs.uk/conditions/nhs-health-check/your-nhs-health-check-results-and-action-plan/

81 This advice is also reflected in guidance from NHS Digital which governs the reporting of uptake and results. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/nhs-health-check-programme/nhs-health-check-programme-supporting-information

82 Freeman ALJ. How to communicate evidence to patients. Drug Ther Bull. 2019;57(8):119-124

83 Spiegelhalter D. Risk and Uncertainty Communication. Annual Review of Statistics and Its Application. 2017;4(1):31-60

84 Edwards A, Elwyn G, Mulley A. Explaining risks: turning numerical data into meaningful pictures. BMJ. 2002;324(7341):827–830

85 Freeman ALJ. How to communicate evidence to patients. Drug Ther Bull. 2019;57(8):119-124

86 Gigerenzer G, Gaissmaier W, Kurz-Milcke E, et al. Helping doctors and patients make sense of health statistics. Psychol Sci Public Interest. 2007;8(2):53–96

87 Freeman ALJ. How to communicate evidence to patients. Drug Ther Bull. 2019;57(8):119-124

Given these issues, stating numbers in a variety of ways is recommended to give people a more balanced view. This is consistent with the CVD risk calculator web tool - QRISK®3 (Figure 3 (L)), which employs a range of formats for presenting the risk under 'Your results': percentages (22.5%); frequency (23 out of 100 people like you); and the icon array displaying the 100 people graphically.

Graphics

Graphics can be used to summarise and clarify numbers, enabling people to 'see' the numbers and appreciate their context.[88] Graphics include line graphs, bar charts and icon arrays. Each of these types of graphics have relative benefits and advantages, but there is some evidence to suggest that icon arrays may be particularly good for communicating risk information to people with lower levels of education and numeracy.[89] This is because they translate percentages into discrete visual units and better communicate the part-to-whole ratio.

Framing

The framing of a risk figure is another important consideration. Equivalent risks can be framed in terms of a positive/gain or a negative/loss, and differences in framing can lead to differences in risk perception. To attempt to circumvent framing effects, it may help to communicate risk information in both positive and negative ways. For example, a 60% risk of developing a condition also means a 40% risk of not developing the condition, or, out of 100 patients with these risk factors, 60 of them will develop the condition and 40 will not.

Adopting a range of written and graphical methods that can cater to individual differences and preferences is consistent with best practice recommendations and the literature on effective risk communication. Clinicians then have the task of using this information to help ensure that patients understand the 'material risks' for them as individuals: a matter not only of probability but also of the impact it could have on them personally. Strategies to assist with this include using multiple formats, paying attention to framing effects and encouraging interactivity as part of the risk communication process.

It is also worth noting that during the Covid-19 pandemic, fewer NHS Health Checks were conducted, and those that were carried out were done by phone or e-consultation. This presents additional challenges in terms of communicating risk information, particularly 'high risk' results.

What will change if polygenic scores are incorporated?

Communicating genetic risk information is a specialised task that requires competence and training. Communicating polygenic risk presents different challenges to the communication of high penetrance rare variants, as the susceptibility aspects of polygenic testing are not significantly different from those of current risk factors such as age, blood pressure and smoking status.[90]

88 Recchia G, Freeman A. Communicating risks and benefits to cardiology patients. Heart. 2020;106:1862-1863

89 Galesic M, Garcia-Retamero R, Gigerenzer G. Using icon arrays to communicate medical risks: overcoming low numeracy. Health Psychol. 2009; 28(2): 210-216

90 Evans JP, Burke W. Genetic exceptionalism. Too much of a good thing? Genet. Med. 2008;10:500–1

Although high penetrance variants have been communicated in clinical genetics practice for decades, and therefore a large body of literature and guidance has been developed to help healthcare professionals to promote patient understanding, communicating polygenic scores is a relatively new endeavour. An additional challenge is that going forward, polygenic risk information for common disorders will be interpreted, communicated and utilised by healthcare professionals whose roles have not traditionally extended to genetics, including those in primary care.

In terms of communicating the absolute risk number itself (i.e. the estimated likelihood overall that the patient will have a heart attack or stroke in the next 10 years of their life), there is little that would need to change if a polygenic score were included alongside the non-genetic risk factors. All of the same best practice principles regarding risk communication would apply; methods of communication would need to be tailored to patient numeracy, literacy and preferences. A growing body of evidence suggests that at least some members of the lay public view genetic information about common disorders the same way they view other medical information, and feel it should be treated similarly.[91,92,93] However, there is also some evidence to suggest that communicating complex genetic information can be challenging especially in terms of readability and the use of unfamiliar terminology.[94]

Healthcare professionals would need additional training, resources or support to be able to answer questions that might arise about the polygenic score 'risk number' component of the overarching risk assessment. In Figure 3 (L), QRISK®3 includes the information that the patient's systolic blood pressure (mm Hg) is 132 and BMI is 31.22 kg/m2 : a patient may ask, "What does it mean that my systolic blood pressure is 132? And what does having a BMI of 31 mean?" Just as the healthcare professional would need to be able to answer these questions, they would also need to be able to answer the questions, "What does it mean that my polygenic score is 40?" or "What does having a high polygenic score mean?"

GPs and other healthcare professionals delivering the NHS Health Check would thus need to have the same level of competency and confidence to answer any questions patients might have about the polygenic score as they do for questions about other risk factors such as blood pressure, cholesterol, obesity and smoking. They would also need to be able to help patients use this information to make risk management decisions going forward (see section 4.4.3).

91 Diergaarde B, Bowen DJ, Ludman EJ, et al. Genetic information: special or not? Responses from focus groups with members of a health maintenance organization. Am. J. Med. Genet. A. 2007;143A:564–69

92 Vermeulen E, Henneman L, van El CG, et al. Public attitudes towards preventive genomics and personal interest in genetic testing to prevent disease: a survey study, European Journal of Public Health. 2014; 24(5): 768–775

93 Lautenbach DM, Christensen KD, Sparks JA, et al. Communicating genetic risk information for common disorders in the era of genomic medicine. Annu Rev Genomics Hum Genet. 2013;14:491-513

94 Lynch JA, Sharp RR, Aufox SA, et al. Understanding the return of genomic sequencing results process: content review of participant summary letters in the eMERGE research network. J Pers Med. 2020; 10(2):38

As highlighted in section 4.2.2, 'just-in-time' rather than 'just-in-case' education and resources related to understanding polygenic scores would need to be developed and delivered to all healthcare professionals involved in carrying out Health Checks. For this to happen the end-to-end pathways need to have been considered, and timelines put in place so that staff are equipped with the right skills at the right time (rather than months or years before clinical implementation). A failure to educate staff about polygenic scores might be a potential barrier to implementation and the successful use of polygenic scores in risk management.

Short online courses, such as those developed by The Winton Centre for Risk & Evidence Communication,[95] may also be valuable resources to help guide healthcare professionals through interpreting and communicating risks that include a genetic component. Courses currently offered by the Winton Centre on communicating potential benefits and harms from genetic testing are focused on rare cancer variants. However, as genetics becomes embedded in primary care, demand for similar courses relating to polygenic risk in this context may rise.

4.4.3 Shared decision-making about risk management

Effective risk communication is critical because it enables shared decision-making about risk management. Shared decision-making (Box 7) is central to risk management in this context because it helps to establish the best course of action for patients and elicit better health outcomes.

Box 7. Shared decision-making

In the context of primary care, informed choice is often facilitated through the verbal process of shared decision-making as well as via written information.

The goal of shared decision-making is to ensure that the patient makes the decision that is right for them. It is a collaborative process through which a clinician supports a patient to make a decision about their healthcare. This combines the clinician's expertise in treatment options, evidence, risk assessment and benefits, with the patient's knowledge of their own preferences, personal circumstances, goals, values and beliefs. The process involves weighing up the available options in light of both of these perspectives.

The importance of shared decision-making is highlighted in key policy documents such as the NHS Constitution 2015.[96] Similarly, all NICE guidance recommends shared decision-making because 'people have the right to be involved in discussions and make informed decisions about their care.'[97]

95 University of Cambridge. 'Winton Centre for Risk and Evidence Communication'. Accessed at https://wintoncentre.maths.cam.ac.uk/

96 Department for Health and Social Care. The NHS Constitution for England (updated 2021). Available at https://www.gov.uk/government/publications/the-nhs-constitution-for-england/the-nhs-constitution-for-england

97 National Institute for Health and Care Excellence. 'Shared decision making'. Key therapeutic topic [KTT23]. March 2019 (updated September 2019). Available from: https://www.nice.org.uk/advice/ktt23

It follows that, in addition to being supported to understand what their risk 'number' means, patients also need to be supported to act on their results where necessary.

Current practice

Returning results within NHS Health Checks requires healthcare professionals to be competent and confident in using the CVD risk calculation tool, understanding and interpreting the results generated, and understanding how these results might inform future management or interventions. They need to communicate the results back to patients, and support patients to understand their results, but also support them to act on their results if this is appropriate.

The importance of this next step (shared decision-making about risk management or risk-reducing action) is reflected in the guidance that has been developed to help healthcare professionals communicate the results from disease risk assessments back to patients. The NHS Health Check programme standards[98] for commissioners and providers state that staff responsible for communicating individual disease risk information to patients should be trained to:

- communicate risk in everyday, jargon-free language so that individuals understand their level of risk and what changes they can make to reduce their risk;
- use behaviour change techniques (such as motivational interviewing) to deliver appropriate lifestyle advice and how it can reduce their risk; and
- establish a professional relationship where the individual's values and beliefs are identified and incorporated into a client-centred plan to achieve sustainable health improvement.

The guidance also states that face-to-face conversations between providers and patients should be supported by:

- individualised written information, including results;
- bespoke advice on the risks identified; and
- self-referral information for lifestyle interventions.

As can be clearly seen, much of the guidance understandably focuses on what happens or should happen next, not only the communication of the risk 'number' itself.

98 Public Health England. NHS Health Check programme standards: a framework for quality improvement. July 2020. Available from: https://www.healthcheck.nhs.uk/commissioners-and-providers/national-guidance/

Shared decision-making about CVD risk management

If the CVD risk assessment identifies the patient's absolute risk of CVD (i.e. of having a heart attack or stroke) over the next 10 years is greater than 10% ('moderate or high risk'), NICE guidance states that the clinician should talk to the patient about whether they want to start taking a statin to manage or reduce their risk.[99]

A NICE patient decision aid is available to support discussions about statin therapy.[100] This decision aid includes information about the process, risks and common side effects of taking a statin, and graphically presents the potential benefits of taking statins at different levels of 10-year risk (from 10% up to 40%). It also includes a table to help patients weigh the issues that are important to them. It is designed for the patient to work through with their healthcare professional but can also be taken home to aid discussions with friends and family. If during the shared decision-making process the patient indicates that they do want to, the GP should then prescribe a statin.

Shared decision-making about management of traits contributing to CVD risk

'Lifestyle' risk factors: Regardless of whether the patient's absolute risk of CVD is moderate or high (i.e. whether or not it reaches the 10-year risk threshold of 10%), NICE guidance states that all patients should be given lifestyle advice.[101] NICE advises that clinicians should assess patients' weight and 'lifestyle' behaviours and support behaviour change where this is needed: for example, obese patients should be signposted/referred to a weight loss program (diet and/or physical activity), and patients who smoke should be referred to a smoking cessation program.

Consistent with this advice, the evidence indicates that the majority of people referred for behaviour change support after an NHS Health Check do not reach the 10% absolute CVD risk threshold (i.e. are at 'low risk' of CVD in absolute terms). As would be expected, the majority of individuals referred for behaviour change support are referred on the basis of their BMI, smoking status or other 'lifestyle' related risk factors rather than their CVD risk profile.[102]

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99 National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical Guideline [CG181]. 2014, updated 2016. Available from: https://www.nice.org.uk/guidance/cg181/chapter/1-recommendations

100 National Institute for Health and Care Excellence. Taking a statin to reduce the risk of coronary artery disease and stroke: patient decision aid. 2014. Available from https://www.nice.org.uk/guidance/cg181/resources/patient-decision-aid-pdf-243780159

101 National Institute for Health and Care Excellence. 'Cardiovascular disease, risk assessment and prevention'. Available from: https://bnf.nice.org.uk/treatment-summary/cardiovascular-disease-risk-assessment-and-prevention.html

102 Robson J, Dostal I, Sheikh A, et al. The NHS Health Check in England: an evaluation of the first 4 years. BMJ Open. 2016;6: e008840

'Physiological/biomarker' risk factors: Similarly, the NHS Health Check Best Practice Guidance[103] states that, if thresholds for individual traits or risk factors are met (e.g. raised cholesterol or blood pressure), this should trigger additional assessments for conditions such as hypertension, chronic kidney disease, cirrhosis or diabetes regardless of the overarching CVD risk assessment result.

When considering shared decision-making about individual risk factor management, it should be recognised that motivating risk-reducing behaviours (in the form of statin adherence or, in particular, lifestyle improvements) is complex and often requires far more than the provision of risk information alone.

There is evidence that some patients make lifestyle changes that they attribute to having attended the NHS Health Check,[104] with some patients describing it as a 'wake-up call'. Other patients, however, state that factors such as their psychosocial circumstances[105] or healthy eating advice being too generic[106] acted as barriers to change. Identifying interventions that might address missing capabilities, motivations and opportunities[107] and developing strategies for implementing these will often be necessary, and might require different sources of support. Some key requirements for effective behaviour change, such as automatic motivation, physical opportunity or social capability, are largely outside of the control of the clinician. This emphasises the need for policy strategies beyond primary care and system level changes to help address wider determinants of health.

What will change if polygenic scores are incorporated?

It is unclear whether or how risk management and the threshold for investigation should change in response to high (or low) polygenic scores. In addition to guidance addressing the overall risk assessment results, NICE provide guidance addressing individual clinical risk factors such as high BMI, blood pressure or cholesterol. Similarly, there will be a need for clear guidance advising clinicians on how to respond to different degrees of polygenic risk should it be incorporated into the risk assessment. This is important because although polygenic scores are stable, disease risk can still be modified by environmental factors, preventative treatments and other interventions.

Generating evidence to inform best practice for those who are identified as having a high polygenic score, particularly in the absence of high lifestyle or clinical risk factors, is an important priority. New guidance and resources would be needed to support shared decision-making in this situation and

103 Public Health England. NHS Health Check Best practice guidance for commissioners and providers. October 2019 (updated March 2020). Available from https://www.healthcheck.nhs.uk/commissioners-and-providers/national-guidance/

104 Usher-Smith JA, Harte E, MacLure C, et al. Patient experience of NHS health checks: a systematic review and qualitative synthesis. BMJ Open. 2017;7(8):e017169

105 Perry C, Thurston M, Alford S, et al. The NHS health check programme in England: a qualitative study. Health Promot Int. 2016;31

106 McNaughton RJ, Shucksmith J. Reasons for (non)compliance with intervention following identification of 'high-risk' status in the NHS Health Check programme. J Public Health. 2015;37: 218–225

107 Michie S, van Stralen MM, West R. The behaviour change wheel. A new method for characterising and designing behaviour change interventions. Implementation Science. 2011. 6; 42

to clarify whether additional interventions are justified, such as increased intensity of interventions coupled with more frequent monitoring. There will also be instances where individuals who are at high risk on the basis of conventional risk factors, are re-categorised due to having low polygenic risk. Clarity around appropriate enhanced or reduced interventions for these borderline cases will be essential.

Shared decision-making about CVD risk management

As is currently the case, GPs would still be advised to discuss statins with patients at greater than 10% 10-year risk of CVD regardless of whether that risk was based on genetic factors, non-genetic factors, or a combination of both genetic and non-genetic factors. The polygenic score would have improved the accuracy of this overall score, providing some increased confidence in the calculation.

It is unclear, however, whether the threshold for statins should be lowered for healthy individuals at high polygenic risk, regardless of their overall risk, as a preventative measure. This is because there is not yet sufficient evidence surrounding the effects of statins in this cohort. It is possible that regardless of the cause of high risk they might benefit from reducing their cholesterol levels and blood pressure.

Incorporating a polygenic score might change the behaviours of healthcare professionals (e.g. strength of recommendation to initiate a statin, and likelihood of prescribing a statin) and/or patients' behaviours (e.g. statin initiation and persistence or adherence over time), either due to or independently of formal guidelines.

As previously noted, evidence indicates that currently only 20% and 9% of patients identified as being at high CVD risk via NHS Health Checks are prescribed a statin or antihypertensive medication respectively.[108] It is conceivable that GPs, when faced with a patient who is 'high risk' based on both genetic and non-genetic risk factors, might more strongly recommend that they start a statin than if the same risk 'number' were based on other risk factors aside from the polygenic score. Indeed Hadley et al suggest that the greatest potential for leveraging clinical utility from the use of polygenic scores may be from changing health professionals' behaviour, rather than by directly motivating patients to change their lifestyle behaviour.[109] This debate remains unresolved in the absence of empirical evidence addressing this question, as current evidence is limited.[110]

Additionally, it is possible that the number of individuals crossing the 10% risk threshold will rise or fall due to the addition of polygenic scores. If this is the case, an assessment may be carried out to decide whether a new value threshold should be implemented, which could include economic and ethical considerations.[111]

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108 Hobson J, Dostal I, Sheikh A, et al. The NHS Health Check in England: an evaluation of the first 4 years. BMJ Open 2016;6: e008840

109 Hadley TD, Agha A, Ballantyne C. How do we incorporate polygenic risk scores in cardiovascular disease risk assessment and management? Current Atherosclerosis Reports. 2021; 23:28

110 Lieb W, Vasan RS. An update on genetic risk scores for coronary artery disease. Are they useful for predicting disease risk and guiding clinical decisions? Expert Review of Cardiovascular Therapy. 2020;18:8: 443-447

111 Pharoah PD, Hollingworth W. Cost effectiveness of lowering cholesterol concentration with statins in patients with and without pre-existing coronary heart disease: life table method applied to health authority population. BMJ 1996, 312(7044): 1443-1448

Decision aids

Decision aids, an important tool in facilitating shared decision-making about risk management, may become even more important with the addition of a genetic risk factor. It will be necessary to develop materials, or adjust existing ones, to inform and support decision-making by health professionals and patients.

In a research setting, Kullo et al adapted an existing statin decision aid to incorporate polygenic score information about CVD.[112] The statin decision aid was developed by the US Mayo Clinic to support and record discussions between clinicians and patients about the risk of having a heart attack over a 10-year period. Kullo et al adapted the decision aid to incorporate a genetic risk score (aka a polygenic score) and to display how this risk could be reduced with the use of interventions such as high or regular dose statins.[113]

The tool generates an icon array, which illustrates the number of patients sharing the patient's risk profile (in terms of blood pressure, cholesterol, genetic risk score, age etc.). It can be used to support and record discussions about the numbers of people who will have a heart attack with the same risk profile as the patient, and thus demonstrate the numbers of people 'like them' who will be 'saved' from a heart attack by taking medicine. In this respect it is similar to the NICE decision aid developed to show the benefits and risks of taking statins in the UK.[114] However, this decision aid compares the disclosure of CVD risk estimates based on conventional risk factors, with risk estimates taking into account the genetic risk score.

Having a tool that incorporates the functionality of showing how one risk factor may contribute to overall risk could be important in supporting discussions between patients and healthcare professionals. However, it may also exacerbate genetic exceptionalism, seemingly giving additional weight to the polygenic aspect of risk.

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112 Kullo I, Jouni H, Austin EE, et al. Incorporating a genetic risk score into coronary heart disease risk estimates. Effect on Low-Density Lipoprotein Cholesterol Levels (the MI-GENES Clinical Trial). Circulation. 2016; 133:1181-1188. [Supplementary material available at https://www.ahajournals.org/action/downloadSupplement?doi=10.1161%2FCIRCULATIONAHA.115.020109&file=020109_supplemental_material.pdf]

113 Ibid.

114 National Institute for Health and Care Excellence. Taking a statin to reduce the risk of coronary artery disease and stroke: patient decision aid. 2014. Available from https://www.nice.org.uk/guidance/cg181/resources/patient-decision-aid-pdf-243780159

Kullo et al also found that those patients who received a genetic risk score following disclosure of coronary heart disease risk, were more likely to initiate statin medication through a process of shared decision-making, although the researchers did not specifically explore the impact of the decision aid. Nevertheless, the disclosure of a polygenic score did not significantly change dietary fat intake, physical activity levels or anxiety, although the lowering of low-density lipoprotein cholesterol (LDL-C) levels was greatest in individuals with a high genetic risk score for coronary heart disease in comparison with participants who did not receive a genetic risk score.

Shared decision-making about management of traits contributing to CVD

Lifestyle risk factors: The incorporation of polygenic scores into CVD risk assessments would not generally change shared decision-making about risk management where a patient has individual CVD 'lifestyle' risk factors: it would still be appropriate to refer the obese patient to a weight loss programme, and the smoker to smoking cessation services.

In instances where patients have low or moderate lifestyle risk factors and a high polygenic score, further encouragement may be given to adopt healthier behaviours, beyond standard lifestyle information. More evidence is needed to demonstrate the effectiveness of this approach.

Clinical risk management of physiological/biomarker risk factors: Similarly, it would still be appropriate to carry out further assessments for patients with very high cholesterol or very high blood pressure. It could be the case though that where an individual has a high CVD polygenic score, extra measures are taken to encourage the patient to lower their other physiological risk factors to below the normal range.

Need for further evidence on impact of polygenic scores on patient behaviours: There is currently a lack of empirical evidence to suggest what impact the inclusion of polygenic scores would have on patient behaviours. Whilst a risk prediction using genomic information in the form of a polygenic score may itself be enough to motivate a small subset of the population to change their behaviour under specific conditions,[115] theoretical models of behaviour change suggest that this needs to be combined with other forms of support.[116] However, there is an absence of large-scale clinical trial data with long term follow-up that is able to demonstrate whether there is a clear impact on risk-reducing behaviours, and reduction of CVD events, among participants whose overall risk and treatment recommendations have been directly informed by both their conventional and genetic risk factors. More research is needed in both a clinical and public health setting to inform future policy.

115 Silarova B, Sharp S, Usher-Smith J, et al. Effect of communicating phenotypic and genetic risk of coronary heart disease alongside web-based lifestyle advice: the INFORM Randomised Controlled Trial. Heart. 2019;105:982-989. This study found that provision of phenotype or genotype risk information alongside web-based lifestyle advice only impacted on self-reported fruit and vegetable intake and did not affect physical activity, health-related behaviours, biological risk factors or emotional well-being.

116 Michie S, van Stralen MM, West R, et al. The behaviour change wheel: A new method for characterising and designing behaviour change interventions. Implementation Science. 2011; 6:42

4.5 Summary

In this section, we have evaluated how each component of the current NHS Health Checks pathway might have to change if a polygenic score were incorporated into the CVD risk assessment process. We have reviewed the existing stages of the patient pathway: inviting eligible patients, the nature and objectives of the NHS Health Check appointment and the return of results to both health professionals and patients.

We conclude that only modest changes would be needed to the information leaflet and NHS website which patients may access in advance of their Health Check appointment, but that more substantial changes would be needed to the infrastructure to support the collection of an additional sample for genotyping, analysis, and return of the result to the healthcare practitioners. Since these occur outside of the current NHS Health Checks infrastructure, we have not analysed these in detail.

Our analysis has highlighted that the most significant changes necessitated by the addition of polygenic scores for CVD risk assessment within NHS Health Checks might be to create new guidance to help healthcare professionals navigate the challenges around risk management for different levels of polygenic risk, and to modify the return of results and decision-making process currently undertaken by healthcare professionals and patients.

Integration of the polygenic score into a risk tool will require adaptation of existing tools to allow for this additional information, weight it appropriately and impute it when necessary.

Most importantly, when healthcare professionals return results to patients, they will need sufficient confidence and competence to be able to understand the polygenic score component and answer any questions that patients may have. At a minimum, this is likely to require just-in-time educational resources about polygenic scores. Using multiple ways to express risk, and framing those risks appropriately are examples of how risk communication can be tailored to the literacy and values of patients, as reinforced by professional guidance.

Our conclusion is that although the integration of polygenic scores into NHS Health Checks would not pose entirely new communication challenges, there would nonetheless be a need for new tools and resources to support understanding of how polygenic scores contribute to overall risk and how their use influences best practices in risk communication. A summary of current NHS Health Checks practice, and the likely changes if polygenic scores were to be incorporated into the existing CVD risk assessment process is set out in Table 1 below.

Table 1. Summary of current NHS Health Checks practice and future potential changes due to incorporation of polygenic scores into CVD risk assessment.

Step	Activity	Current practice	What will need to change?
1	Identification of eligible patients	Healthcare professional (HCP) undertakes a systematic search of patient databases for adults aged 40-74 without heart disease or a related condition, or invites patients opportunistically	No change required. However, prioritising invitations within this target age group could be informed by PGS
2	Invitation, informed choice and the decision to have a Health Check	**Invitation and written information** ■ Formal invitation letter is sent from GP practice, or an appointment is arranged ad hoc ■ Some GP practices send out a standardised PHE information leaflet ■ NHS website provides basic information to help patients make a decision **Decision to attend** Patients makes an active or passive decision to attend on the basis of these sources of information and/or other factors. In some instances this may be supported by a conversation with the GP	**Invitation and written information** Invitation letter will not need to change; brief information about polygenic scores will need to be added to the information leaflet and to the NHS website alongside the other risk factors listed **Decision to attend** GP and nurse practitioner education about polygenic scores will be needed e.g. via Health Education England (HEE)
3	The NHS Health Check appointment	Over the course of one or two appointments, the HCP (typically a GP, nurse practitioner or healthcare assistant) collects information about the individual's lifestyle and family history, measures their height and weight, takes their blood pressure and draws a blood sample. Consent is implied by patient actions (e.g. attending the appointment, extending arm for blood to be taken)	An additional DNA sample would need to be taken, sent to a lab for genotyping and analysis, and a 'score' returned to the HCP

Step	Activity	Current practice	What will need to change?
4.1	Return of results: risk presentation to the healthcare professional	Risk factors from the patient's electronic health record are manually or automatically uploaded to the CVD risk calculator tool, which presents the risk result to the HCP as a percentage	The polygenic score will need to be returned to the HCP, and the CVD risk calculator tool adapted to include this new risk factor
4.2	Return of results: risk communication to the patient	HCP communicates the CVD risk result to the patient. (Best practice advises using a range of methods descriptive/numerical/ graphic)	HCP will need confidence/ competence to communicate the polygenic score to patients and answer questions about the polygenic score risk factor in the risk result
4.3	Return of results: shared decision-making about risk management	**Lifestyle risk management** Depending on lifestyle risk factors the GP/HCP provides or refers the patient for stop smoking services, weight management services etc **Clinical risk management (individual risk factors)** Depending on clinical risk factors (blood pressure etc.) GP carries out additional tests and/ or recommends prescribing medication **Clinical risk management (based on 10-year risk calculation)** If >10% ('moderate risk'), GP/ HCP discusses risk-reducing medication, e.g. statin, with patient, as well as lifestyle changes if relevant. They might prescribe a statin and/or refer on to lifestyle change intervention **Patient** Patient decides whether or not to accept referral to services and/or medication prescription	**Lifestyle risk management and clinical risk management (individual risk factors)** This will not need to change. However, clear guidance advising clinicians on how to respond to different degrees of polygenic risk will be needed, as it may impact on the nature/ intensity of clinical or lifestyle risk factor management **Clinical risk management (based on 10-year risk calculation)** If >10% ('moderate risk') will not need to change **Patient** It remains the patient's right to choose whether or not to accept referral to services or a prescription for medication. Understanding the rationale for these can increase patient uptake **General** HEE just-in-time resources/ education based on revised guidance will be needed

5. Future prospects

In this final section of the report, we consider how the implementation of polygenic scores for CVD as part of NHS Health Checks might be extended beyond the more modest changes described in section 4. This includes potential opportunities for detecting and preventing CVD beyond what is currently provided as part of that programme. It is timely to reflect on whether the changes that might be recommended as a consequence of the NHS Health Check Programme review (Box 4) could generate additional questions about the optimal timing of those interventions, the associated risks and benefits, and wider operational aspects.

5.1 Emerging policy developments

The potential for polygenic scores to inform more targeted prevention and treatment through increased 'risk stratified' screening is now firmly part of the policy agenda.[117] Polygenic scores are noted as a potentially useful tool for preventative efforts and adopting a population wide prevention strategy using genomics at scale is consistent with the strategic objectives of Genome UK: The Future of Healthcare.[118] This approach will be supplemented by population wide longitudinal cohort research such as that envisaged by the Our Future Health research programme which aims to recruit a population cohort of 5 million participants (Box 8).[119] At least 3 million of the participants in this programme will have their polygenic scores calculated for a number of diseases, including CVD. One of the overall objectives of this aspect of the research programme is to enable an evidence-based position on whether and how polygenic scores can be best utilised at scale in the health service.

Box 8. The Our Future Health Research Programme

In 2019, Our Future Health (previously named Accelerating Detection of Disease) was launched as part of the Life Sciences Industrial Strategy and will be the UK's largest ever health research programme. It has been established as a collaboration between the public, charity and private sectors and will create a world-leading resource for health researchers, to enable the discovery and testing of more effective approaches to prevention, earlier detection and treatment of diseases.

The programme will carry out up to five million polygenic risk score assessments on volunteers, who will each be offered personalised feedback on their results. It will link phenotypic data to longitudinal biological samples available for research purposes.

117 Richards M. Report of the independent review of adult screening programmes in England. Oct 2019. Available from: https://www.england.nhs.uk/wp-content/uploads/2019/02/report-of-the-independent-review-of-adult-screening-programme-in-england.pdf

118 Genome UK: the future of healthcare. September 2020. Available from: https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare/genome-uk-the-future-of-healthcare

119 Office for Life Sciences. Life Sciences Industrial Strategy Update. January 2020. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/857348/Life_sciences_industrial_strategy_update.pdf

The data created will allow evaluation of new polygenic risk scoring across millions of volunteers to see if and how they can be incorporated into smarter, more targeted clinical trials, research, and screening programmes. The resulting data will be made available to approved researchers from academia and industry, with the goal of creating a rich and comprehensive dataset. The following resources will be created:

- a prospective observational dataset for basic science/epidemiological, discovery and aetiological research e.g. on the causes and early signs of disease; and
- a translational research platform comprising a cohort of people who can be re-contacted for translational/implementation research to develop and test new diagnostic technologies, prevention strategies and treatments.[120]

Their findings will be highly relevant to the implementation of polygenic scores, both within the NHS Health Check programme, and if preventative efforts are broadened, as described below.

5.2 Potential changes to the CVD risk assessment landscape within NHS Health Checks

The imminent NHS Health Check Review is likely to address improvements that could be made to the current programme. Although the rates of attendance for NHS Health Checks have increased over time, from the introduction of the programme in 2009, through to it being a statutory obligation to be offered by local authorities in 2013, a recent review noted that 52.6% of patients took up the offer to attend an NHS Health Check over the five year cycle between 2012 and 2017.[121] However, this figure does not reflect marked geographical variation in uptake, with the percentage of invited individuals attending an NHS Health Check ranging from 25.1% to 84.7%. Of those who had a CVD risk score documented, 25.9% had a 10-year CVD risk of ≥ 10% (i.e. at moderate or high risk) of which 20.3% were prescribed a statin.[122] Despite the variability in attendance, this review found little or no evidence of inequity in either processes or uptake,[123] but it is acknowledged that in order to fully achieve the anticipated benefits of the NHS Health Check programme further efforts are needed.

Improvements could be made through increasing general uptake to the programme, or by targeting those who are at greater risk, who may have most to gain from potential intervention. For example, modelling by Mytton et al demonstrated, in the context of NHS Health Checks, that ensuring those who are assessed and eligible for statins receive them is an important strategy to increase benefits.[124] However, this could also include using polygenic scores in a targeted way within the existing NHS

120 Personal communication from the Our Future Health project, July 2021.

121 Patel R, Barnard S, Thompson K, et al. Evaluation of the uptake and delivery of the NHS Health Check programme in England, using primary care data from 9.5 million people: a cross-sectional study. BMJ Open. 2020;10:e042963

122 Ibid.

123 Ibid.

124 Mytton O, Jackson C, Steinacher A et al. The current and potential health benefits of the National Health Service Health Check cardiovascular disease prevention programme in England: A microsimulation study. PLoS Med. 2018 Mar 6;15(3):e1002517

Health Check framework, or using them independently, potentially at an earlier age, to target those who should be invited.

5.2.1 Targeting those currently at intermediate risk within NHS Health Checks

Although a targeted approach to the use of polygenic scores within NHS Health Checks could be more efficient than cohort wide use, knowing who to target and on what basis is key. Various studies have modelled the impact of offering results from polygenic score analysis to those at intermediate risk using traditional risk factors. Improved discrimination through adding polygenic scores could inform management of this group, and those at the highest risk will already be eligible for interventions mitigating their potential risk. A similar targeted approach could be adopted within the NHS Health Check programme, focusing only on those people judged to be at intermediate 10-year risk of CVD after initial screening with conventional risk factors alone.

A recent study by Sun et al[125] analysed over 300,000 participants from the UK Biobank, without a history of CVD who were not taking lipid-lowering medication and found that additional benefit can be derived from utilising polygenic scores in this group of individuals who are at intermediate risk. Their modelling suggests that such targeted assessment could reclassify approximately 12% of screened individuals to the high risk category, of whom 11% would be expected to have a CVD event within 10 years. Furthermore, the researchers found that if this targeted approach were coupled with the initiation of statin therapy in accordance with NICE guidelines (i.e. those with 10-year CVD risk of 10% or more), 1 extra CVD outcome could be prevented over 10 years for approximately every 340 people at intermediate risk in whom polygenic scores are assessed. This compares with the need to screen approximately 5,700 people to achieve the same gain when using a blanket screening approach.

Overall, they concluded that a targeted strategy could help prevent 7% more CVD events than conventional risk prediction alone. Based on these predictions, focusing polygenic score analysis on those at intermediate risk is more efficient than a blanket approach. However those who are categorised as low or high risk based on conventional risk assessment, and who might still gain some benefit from knowing their polygenic score, would not receive it under this model.

5.2.2 Polygenic risk assessment for CVD at an earlier age

One of the highly debated applications of polygenic scores is their use earlier in life to identify those who are potentially at high risk, enabling more effective prevention. While almost all of the non-genetic risk factors for CVD emerge over the life course (e.g. high blood pressure, high cholesterol, and indeed age itself), genetic risk can be quantified at birth and is stable over time. This is useful in the context of CVD risk assessment as polygenic scores could help to identify high risk individuals long before phenotypic risk factors develop.

125 Sun L, Pennells L, Kaptoge S, et al. Polygenic risk scores in cardiovascular risk prediction: A cohort study and modelling analyses. PLoS Med. 2021;18(1): e1003498

Whilst there may be little benefit in bringing forward the age at which the entire NHS Health Check is carried out (as younger cohorts are unlikely to present as high risk through conventional risk factors because signs of disease will not be evident), one direction of travel may be that a standalone polygenic risk assessment is carried out at an earlier age.

There is much debate about what age to do a polygenic score analysis, with some interviewees expressing the view of 'the earlier the better' when it comes to polygenic risk assessment. Different screening scenarios, from newborn through to early adulthood, raise different considerations. There is evidence that bringing the age of testing forward (from 40 to 18 or 30 years) could have value, as plaque build-up in the vasculature (atherosclerosis) can begin at an early age (pre-teen) and stay with individuals for life.[126] Testing in these presymptomatic young adults could provide the earliest indication of a predisposition to such build-up, allowing preventative action to be taken in high-risk individuals from a younger age, rather than waiting until 40 when other risk factors are already established. Insights from ongoing research studies and programmes, such as the Our Future Health programme (Box 8), might generate evidence of the effectiveness of this strategy.

This application of polygenic scores relies upon their use as an indicator of disease risk. Since common diseases arise due to a mix of genetic and environmental factors, there is scepticism among some about the standalone use of polygenic scores to predict risk for common disease with a known large environmental component.[127,128] Risk is also subject to change as a result of environmental exposure over time. Therefore assessment of environmental impacts throughout life together with monitoring of phenotypic risk factors would likely be required in addition to early-stage risk prediction, especially for any interventions which may have side effects, or those that are more costly.

The added benefit of assessing polygenic risk has been questioned given that healthy lifestyles should be adopted at a population wide level and not just be restricted to those at high polygenic risk, especially as the majority of disease risk can often be attributed to lifestyle related factors. Establishing the age at which polygenic score analysis might add the most value is likely to require more diverse studies potentially using novel research paradigms that take account of the lack of conventional markers in individuals who have not yet developed detectable disease pathology. This might include using additional endpoints such as age of onset of premature incident CVD.[129] More work is also needed to determine their cost-effectiveness.

5.2.3 Personalised approach to risk estimation using 10-year, 30-year or lifetime risk

As described in section 3.2.1, current approaches to disease prevention and screening tend to use the risks of experiencing a disease 'event' (e.g. heart attack) or being diagnosed with the disease in question within the next 10 years, as a measure of disease risk. In order to be embedded in the risk prediction tool, polygenic score analysis is likely to use the same risk estimation time frame. In the

126 Hong YM. Atherosclerotic cardiovascular disease beginning in childhood. Korean Circ J. 2010; 40(1):1-9

127 Figueroa JF, Frakt AB, Jha AK. Addressing Social Determinants of Health: Time for a Polysocial Risk Score. JAMA. 2020; 323(16):1553-1554

128 Wald NJ and Old R. The illusion of polygenic disease risk prediction. Genet Med. 2019 Aug; 21(8): 1705-1707

129 Levin MG, Rader DJ. Polygenic Risk Scores and Coronary Artery Disease: Ready for Prime Time? Circulation. 2020; 141(8): 637-640

future, NHS Health Checks may adopt a more personalised and flexible approach that allows for the use of different risk estimation metrics (e.g. 10-year risk, 30-year risk, lifetime risk) depending on the individual patient.

The QRISK® risk assessment tool, recommended by NICE guidance, generates a percentage risk of a CVD event in the next 10 years. There are advantages to this approach. A 10-year horizon is useful for clinicians when considering the best management options for a patient. However, using a 10-year relative risk systematically undervalues predicted risks in younger groups, and those who are middle aged but at lower relative risk.[130] Indeed, American guidelines on primary prevention of CVD advise that in individuals aged 20-39 years, and for those individuals aged 40-59 years who are at medium risk (i.e. not at elevated (≥7.5%) 10 year risk), estimating lifetime or 30-year CVD risk may be considered.[131]

For younger patients who have a low absolute 10-year risk but who have a high relative risk compared to their peers, receiving a low 10-year absolute risk could be falsely reassuring.[132] This could miss a potential prevention opportunity in individuals with low to moderate CVD risk who have a number of modifiable risk factors such as smoking, obesity and hypertension.

Lifetime risk estimates, measuring the cumulative risk of developing disease during the remainder of an individual's life, would reflect this relatively high risk and may provide a more appropriate assessment of future risks than estimates limited to 10 years.

This is evidenced by studies that have shown that individuals with a high 30 year risk may not be identified using a 10 year risk prediction.[133,134] Using a 10-year relative risk may also overestimate cardiovascular risk in elderly individuals since competing non-cardiovascular mortality risk may not be adequately accounted for.[135] For younger patients, using a 30-year cardiovascular disease risk might

130 Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart

131 Ibid.

132 Marteau TM, Lerman C. Genetic risk and behavioural change. BMJ. 2001;322:1056–1059

133 Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation. 2006;113:791-798

134 Pencina MJ, D'Agostino Sr RB, Larson MG, et al. Predicting the 30-year risk of cardiovascular disease: the Framingham Heart Study. Circulation. 2009;119:3078-3084

135 Rossello X, Jannick AN, Janssen A, et al. Risk prediction tools in cardiovascular disease prevention: A report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). European Heart Journal: Acute Cardiovascular Care. 2019; 9(5): 522-532

have utility over three decades of assessment (assuming assessments from age 40-74) suggesting the potential for polygenic scores to be used as part of a package of longitudinal risk assessments that would be able to identify risk better in younger people, and be adopted iteratively throughout an individual's life course.[136]

As highlighted earlier in sections 4.4.2 and 4.4.3, calculating and communicating more accurate individual scores does not, in itself, ensure increased interventions such as statin prescription by health professionals, or risk-reduction through individuals changing their behaviour.

More work needs to be done to determine which individuals and groups respond positively to different risk prediction time frames, and how best to support people to reduce their risk. This will include accumulating evidence on whether early intervention in those with a high lifetime risk but low short term risk would have a greater clinical benefit than later intervention, or whether people at low absolute risk would value long term treatments with little short term gain.[137]

Flexibility to use either or both of these risk prediction metrics may lead to higher levels of prescription but also higher levels of intervention adherence. This suggests a need for a more nuanced approach that responds to the patient's age and aggregate risk status coupled with longitudinal evaluation of these interventions.

5.2.4 Constructing multiple polygenic scores for different subgroups

Recent research highlights increasing potential for generating more targeted polygenic scores for different subpopulations defined by age, sex or ancestry background. A recent study[138] examined the clinical utility of an integrated genetic and clinical risk prediction tool both overall, and across a broad array of age-by-sex subgroups. It found that the performance of the polygenic score varied significantly by age. They found evidence in men, but not in women, that predictive power is highest at younger age groups, and declines for older ages.

When comparing the integrated tool against QRISK® there were also substantial differences by age and sex in the overall number of people that are reclassified by the integrated model, with the overall rate peaking in men at 50-54 years old and in women at 65-69 years old. Once sufficient data are available, the use of more granular polygenic scores for different groups will further improve predictive power.

5.2.5 Targeting using scores specific to different CVD subtypes and associated traits

However, in the short-term, the most likely clinical scenario is that a single polygenic score for CVD will be incorporated into NHS Health Checks. This score may be portrayed as generic, but as discussed above, many polygenic scores for CVD are in fact for a specific CVD related condition such as CAD or stroke. Polygenic scores for specific groups of cardiovascular conditions e.g. stroke or

136 Naylor M, Brown KJ, Vasan RS, et al. The molecular basis of predicting atherosclerotic cardiovascular disease risk. Circulation Research. 2021; 128(2): 287-303

137 Hippisley-Cox J, Coupland C, Brindle P. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database, BMJ. 2010;341:c6624

138 Riveros-Mckay F, Weale ME, Moore R, et al. An integrated polygenic and clinical risk tool enhanced coronary artery disease prediction. Circulation: Genomic and Precision Medicine. 2021;14:e003304

CAD, are being developed, as are scores for conditions associated with CVD, such as type 2 diabetes, hypertension and chronic kidney disease. As increasing amounts are learnt about the pathology of atherosclerosis and the pathology of CVD, polygenic scores could be used as part of a new paradigm of multi-parametric, longitudinal risk assessments that would be adopted iteratively throughout an individual's life course.[139]

Research is also being conducted to examine the relationship between polygenic scores and susceptibility to complex physiological/physical traits such as obesity, cholesterol and high blood pressure, and polygenic scores are being developed for each of these traits. Polygenic scores for traits that contribute to a variety of diseases could be a useful (although imprecise) predictor of future disease risk. Obesity, for example, contributes substantially to the development of many diseases and detecting a high genetic susceptibility to obesity could act as an early warning sign.

In the medium term:

- polygenic scores could be calculated for complex or intermediary traits that are risk factors or contribute to that disease/condition
- a single genotyping test could be used to generate multiple polygenic scores for numerous diseases, traits and subtypes of disease

This would allow polygenic scores for a range of cardiovascular conditions, along with associated traits, to be entered into a risk prediction model to generate a more personalised risk prediction score which will refine and improve risk prediction for CVD. However, as well as understanding how individual risk factors act independently and together to cause disease within and between groups which have been stratified by polygenic scores,[140] other measures could be taken to tailor polygenic score analysis to the needs of individuals.

5.3 Beyond NHS Health Checks

NHS Health Checks are currently limited to those aged 40 and over. Offering a polygenic score for CVD below that age would allow more personalised assessments to be conducted earlier. These could target those at increased risk due to genetic risk, pre-existing disease or existing clinical risk-factors, or family history of relevant disease.

139 Genome UK: the future of healthcare. September 2020. Available from: https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare/genome-uk-the-future-of-healthcare

140 Validation of this integrated score might be a challenge as most risk prediction algorithms are validated for use within a specific age range, whereas the polygenic element might be valid throughout the entire lifetime. Lieb W, Vasan RS. An update on genetic risk scores for coronary artery disease. Are they useful for predicting disease risk and guiding clinical decisions? Expert Review of Cardiovascular Therapy. 2020;18:8: 443-447

5.3.1 Use in those currently excluded from NHS Health Checks

Those who have pre-existing disease (which could be a risk factor for developing CVD) such as diabetes, hypertension or chronic kidney disease are currently diverted out of the NHS Health Check programme into the appropriate primary care pathways for treatment and risk management. Polygenic scores could also be utilised in these groups as part of their clinical management. Targeting those who are at increased risk through having higher polygenic risk or due to family history of relevant disease, could be an additional approach.

Those with existing disease, for whom lifestyle changes and drug management is important, may also benefit from polygenic score analysis which might enable a more targeted personalised approach incorporating statin prescription, initiation or intensification.[141] In these patients, treating or modifying these risks may have additional clinical utility through ameliorating the risks of CVD arising.

In addition, Fahed at al found that polygenic background modifies the penetrance of monogenic variants for tier 1 genomic conditions.[142] These are conditions that have significant potential for positive impact on public health based on available evidence-based guidelines and recommendations, and include familial hypercholesterolaemia, hereditary breast and ovarian cancer syndrome and Lynch syndrome.[143] However many of the common variants that predispose to CAD, do so by different pathways than the monogenic variants (such as by inflammation, cellular proliferation and vascular tone).[144] As this paper notes, there are many additional pathways yet to be discovered, and much more evidence is needed to understand how polygenic factors interact with monogenic and environmental factors in causing disease.

5.3.2 Expanding use of polygenic scores beyond primary care

Many of our interviewees described their ambition for polygenic scores to be used across multiple ages and settings as a way of increasing the opportunities for personalised prevention. As part of this vision, the range of actors involved is likely to evolve from use within health systems using existing models of care, through enhanced roles for other health professionals such as pharmacists, or involvement of commercial organisations.

In the context of CVD, research has suggested that an expansion of pharmacist roles could enhance patient support and foster patient adherence. A systematic review of pharmacist-directed and pharmacist collaborative care, demonstrated the benefit of pharmacist care interventions in the management of major CVD risk factors among outpatients.[145] Pharmacists may also facilitate

141 Ye Y, Chen X, Han J et al. Interactions between enhanced polygenic risk scores and lifestyle for cardiovascular disease, diabetes and lipid levels. Circulation: Genomic and Precision Medicine. 2021 14(1):

142 Fahed AC, Wang M, Homburger JR, et al. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. Nat Commun. 2020 Aug 20;11(1):3635

143 Centers for Disease Control and Prevention. Tier 1 Genomics Applications and their Importance to Public Health. Available from: https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm

144 Fahed AC, Wang M, Homburger JR, et al. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. Nature Commun. 2020 Aug 20;11(1):3635

145 Santschi V, Chiolero A, Burnand B, et al. Impact of pharmacist care in the management of cardiovascular disease risk factors: a systematic review and meta-analysis of randomized trials. Arch Intern Med. 2011; 171(16): 1441-1453

patient adherence to long-term statin treatment given that about half the patients prescribed this discontinue statin therapy within one year, often due to adverse events arising.[146]

Expanding the range of health professionals potentially generating and accessing polygenic scores highlights the need for educational resources that extend outside traditional primary care settings. These professionals will need to understand the potential utility of using these scores especially if they are used in isolation outside the primary care setting. Professionals may also need to understand how a score falling at the upper extreme (indicating that the person is at extremely high risk) could be misinterpreted by others if it is seen as deterministic. This illustrates the continuing challenges of mainstreaming genetic and genomic testing into existing risk assessment programmes.

5.4 Summary

Our analysis has highlighted a variety of different applications of polygenic scores to inform CVD risk assessment. These include potential applications within the NHS Health Check programme and beyond. Polygenic scores feature in numerous population scale research programmes, including Our Future Health, which utilise polygenic scores as part of their research methodology. They are also likely to be part of the forthcoming review of the NHS Health Check programme.

Within the NHS Health Check programme, our research suggests that the added value from polygenic scores might be optimised by targeting those at intermediate risk. This is on the basis that those at highest risk will already have access to potentially beneficial interventions. However, in order to optimise the results from stratification within NHS Health Checks, clear guidelines need to be formulated to address how best to manage those people who have high polygenic scores in the absence of other risk factors.

Beyond NHS Health Checks, a number of additional approaches could be adopted: one possibility is to target those who are at increased risk on the grounds of their known pre-existing risk factors, their family history, or through other relevant risk factors such as concurrent disease. An increasingly diverse patient group will necessitate personalised approaches in selecting applicable risk estimation periods and risk tools. This increased complexity may also warrant increased training and support being made available to professionals offering these interventions, especially if these are offered beyond primary care.

146 Maningat P, Gordon BR, Breslow JL. How do we improve patient compliance and adherence to long-term statin therapy? Curr Atheroscler Rep. 2013; 15(1): 291

Conclusions

The NHS Health Check programme is a population scale preventative risk assessment programme aimed at early detection of a range of chronic diseases including cardiovascular disease, type 2 diabetes and stroke. It achieves this through assessing a range of factors known to impact the risk of developing these diseases. Since the ambition is that this programme is accessible to all asymptomatic adults aged 40-75, the existing programme and infrastructure provides an exemplar for delivering polygenic score analysis for cardiovascular disease.

This report therefore addresses how polygenic score analysis for CVD could be implemented into the NHS Health Check programme as a potential route to providing polygenic score analysis at scale within the population of adults in England and Wales. It assumes that the mechanism for delivering polygenic scores to individuals will be primarily using existing NHS Health Check pathways, infrastructures and workforce. In this report we make the assumption that the use of polygenic score analysis in this population has clinical validity and utility. Although the evidence base concerning the clinical validity and utility of polygenic score analysis for CVD is growing, more work is needed to prove demonstrable validity and utility, especially across the diverse ethnic groups within the population.

Our analysis suggests that polygenic score analysis could be incorporated into NHS Health Checks with only modest changes relating to the interface between health professionals and patients. If polygenic score analysis were introduced, existing patient-facing NHS systems and processes involving healthcare professionals and patients would require some minor changes. These include changes to materials supporting informed choice (e.g. patient information leaflets, and patient-facing websites). 'Just-in-time' resources would need to be developed for healthcare professionals delivering the assessments. However, the nature and scale of these changes is more significant than those made following the introduction of other new factors to the existing panel (for example, the addition of a diagnosis of migraines or severe mental illness when QRISK®2 was updated to QRISK®3). Just as for other risk factors, health professionals will need to understand the broad nature of the test being offered, the top-level risks and benefits, and where to find more information if this is requested by the patient. However, the unfamiliarity of polygenic data compared to other risk factors highlights the need for clear risk communication as part of shared decision-making.

In terms of risk management, healthcare professionals will need clear guidance advising them on how to respond to individuals at different degrees of polygenic risk. This is particularly important in instances where a patient is at low risk on the basis of conventional risk factors but has a high polygenic score.

In order to support these changes, a testing infrastructure would need to be developed to enable timely genotyping and return of results conforming with appropriate quality management. Any new pathways would need to be piloted and validated and quality metrics assured. We have not examined the changes that might be required to the wider testing infrastructure in detail, since these are likely to be contingent on other factors that are beyond the scope of this report.

Our work has highlighted the need for intensified research efforts in a number of areas. More evidence is needed of the impact of polygenic score analysis on healthcare provider behaviour, particularly the impact of a high polygenic score on the likelihood of a health professional offering a statin prescription or recommending lifestyle or behaviour change. The nature of the conversations between health professionals and patients about these interventions may also affect patients' understanding of polygenic scores and of the long and short-term impacts of behaviour change (including lifestyle change and statin adherence/compliance). Wider factors influencing public opinion, engagement and trust relating to the use of genetic information within health systems, may also impact the acceptance and use of this novel biomarker.

Although the short-term impacts of incorporating polygenic score analysis into NHS Health Check seem relatively modest, the medium-term impacts could be more significant. Tailoring the risk-assessment process to suit individual patients or sub-groups implies a much more varied and complex landscape, and one that potentially moves the process outside of the existing NHS Health Check programme and infrastructure. This approach could utilise different polygenic score models and risk estimation windows (5, 10, 30 years or lifetime risk estimates) to produce a plethora of potential patient pathways. If this is coupled with offering polygenic scores outside the existing NHS Health Checks infrastructure, this could facilitate more targeted interventions to those at greater risk of CVD, and ultimately provide greater clinical utility in the medium term. In the longer term, embedding a prospective personalised prevention service across a wide age range would be a bigger challenge. Potentially this would require moving risk assessment outside of primary care, possibly involving a dedicated workforce and infrastructure. Understanding the consequences for risk communication of these different routes for different ages and risk groups will be an ongoing challenge.

If health systems choose to adopt personalised risk assessment incorporating polygenic score analysis, a key priority will be to address any inequalities and inequities that might arise, and to proactively mitigate against these. In principle, the implementation of polygenic score analysis into the NHS Health Check programme seems feasible: however implementing these personalised approaches potentially raises more fundamental scientific, cultural and political questions which touch upon wider societal expectations about the nature of the health service as a disease treatment or prevention service.

Appendix 1: Interviewees

The desk-based research underpinning our analysis was supplemented by eight semi-structured interviews. We thank the following interviewees for their time, engagement, and expert insights:

Name	Job title	Organisation
Prof Sir John Bell	Regius Professor of Medicine	Oxford University
Dr Michelle Bishop	Education Development Lead for the Genomics Education Programme	Health Education England
Prof John Deanfield	Professor of Cardiology	University College London
Dr Judith Hayward	GP and Primary Care Advisor	Health Education England
Dr Mike Inouye	Director of Research	Department of Public Health and Primary Care, University of Cambridge
Prof Paul Pharoah	Professor of Cancer Epidemiology	Department of Public Health and Primary Care, University of Cambridge
Dr Juliet Usher-Smith	GP and University Lecturer in General Practice	Department of Public Health and Primary Care, University of Cambridge
Dr Jo Waller	Reader in Cancer Behavioural Science	King's College London

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