D2.2. Evidence for the clinical utility of biomarkers for the prevention of cancer, cardiovascular and neurodegenerative diseases.

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Abstract

Introduction: Personalised medicine and prevention are gaining traction within the context of health system strategy and delivery of care. Measures developed for personalised prevention, especially for chronic conditions such as cancer, cardiovascular diseases (CVD) and neurodegenerative diseases can be supported by the development of biomarkers that can identify individuals at risk of disease.

Aim: To undertake research and analysis to establish the level of evidence for clinical utility for personalised prevention of biomarkers identified in Task 2.1.1. in three disease groups: cancer, CVD and neurodegenerative diseases.

Methods: A prioritised biomarker list was created from the results of Task 2.1.1 based on the quality of research evidence. Test definitions were then established for each of the biomarkers in the prioritised list. Searches for these tests were conducted in relevant databases: Guideline Central; TRIP Pro; NIHR CRD database; International HTA database; and CEA registry, to identify guidelines or HTAs and CEAs indicating evidence supportive, or not, of clinical utility. General searches for genetic testing and polygenic risk scores for each disease group were also carried out.

Results: In cancer, 113 tests utilising 82 unique biomarkers were defined, of which 22 had evidence – 15 supportive and seven not supportive of clinical utility. Most tests with evidence for clinical utility were based on genetic biomarkers for familial cancers, namely prostate and colorectal cancers. For CVD, 59 tests utilising 33 unique biomarkers were defined, of which eight tests had evidence of clinical utility. These tests frequently considered longer-term risk prediction for CVD events and were associated with small changes to existing established tests or models (four tests) or were multi-factorial models (four tests). In neurodegenerative diseases, 32 tests utilising 25 unique biomarkers were defined. Evidence was found for one test only, and it was not supportive of clinical utility.

Conclusion: Our results demonstrate the evidence gaps between the research and translation of promising novel biomarkers for prevention into clinical care. Urgent attention to this gap and further initiatives are needed to accelerate the development of improved prevention interventions and programmes for the European population.

Keywords

Personalised prevention, precision medicine, biomarkers, cancer, cardiovascular diseases, neurodegenerative diseases, chronic diseases, non-communicable diseases.

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Table of contents

PROPHET
a PeRsOnalized Prevention roadmap for the future HEalThcare
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PROPHET a PeRsOnalized Prevention roadmap for the future HEalThcare
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Executive summary

Introduction: Personalised prevention utilises health information from multiple sources including genotypic and phenotypic data, environmental exposure, and lifestyle determinants to tailor an individual's health care. This model of prevention aims to predict the risk of disease or of disease progression or recurrence, along with enabling delivery of personalised care to improve individual outcomes. This could prevent development of disease, increase healthy life expectancy and reduce the burden on the healthcare system.

The focus of personalised prevention initiatives on non-communicable diseases (NCDs) reflect their high mortality and morbidity. NCDs account for approximately 80% of disease burden in the European Union (EU), with circulatory disorders and cancer accounting for almost 3 million deaths in Europe in 2019.

Biomarkers, measurable biological indicators of health and disease, can be used for personalised prevention by identifying those at risk of disease. However, their implementation in healthcare pathways requires comprehensive assessment of their clinical validity and clinical utility. There are various definitions of clinical utility, for the PROPHET project clinical utility is defined as:

"*Clinical utility of a test refers to the likelihood that it provides information that is of value to the person being tested to identify if an effective intervention or preventive strategy is required*".

Determining clinical utility of a biomarker is a complex process. The domains of clinical utility considered under different evaluation frameworks varies. Few evaluation frameworks define the level of evidence required for clinical utility to be satisfied.

Aim of research study: The aim of Task 2.1.2 is to undertake further analysis and research to establish the level of evidence for clinical utility for personalised prevention of the biomarkers identified in Task 2.1.1 and outlined in D2.1.

Methods: Biomarkers identified in systematic reviews with meta-analyses, randomised control trials (RCTs) and reviews (scoping, systematic and umbrella) from the scoping reviews in Task 2.1.1 were prioritised for further research. To assess clinical utility, test definitions for personalised prevention were developed based on the prioritised biomarkers identified in cancer, cardiovascular disease (CVD) and neurodegenerative diseases. Each test definition included the following elements:

- A biomarker
- For a particular disease (WHAT)
- In a particular population (WHO)
- For a particular purpose (WHY)

If a test definition could not be determined, the biomarker was excluded from this analysis.

We considered guidelines to be the highest level of evidence since clinical utility assessment is an integral part of the process of guideline development. In contrast, HTAs and CEAs provide evidence for the assessment of clinical utility. A comprehensive and well-defined database search for high quality evidence was performed using each test definition. The

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databases used were Guideline Central, TRIP (with Pro subscription), Centre for Reviews and Dissemination (CRD) database, the International HTA database and the Cost-Effectiveness Analysis (CEA) Registry.

The search results for a specific test definition were recorded in a standard template and then summarised in a short report for each test including the details of the search. Test definitions were pooled into one report when only the population or disease of interest varied.

In addition, we performed broader searches covering genetic testing and polygenic risk scores (PRS) to investigate the current position of the use of genetic tests and PRS in prevention for the three disease groups.

Results

Cancer: Of the 843 papers identified in Task 2.1.1, 57 were selected for further analysis. From these articles, 82 unique biomarkers were extracted and 113 test definitions were created. The majority of the test definitions covered breast, prostate, liver and gastric cancers. Following the searches evidence regarding clinical utility was found for 22 of the tests. Fifteen of these tests had evidence of clinical utility and seven had evidence showing that the test did not have clinical utility.

Most tests with evidence for clinical utility were based on genetic biomarkers for familial cancers, namely prostate and colorectal cancers. This demonstrated that these high-risk familial variants are already incorporated into clinical practice for preventive measures in high-risk patients, however we did not find evidence supporting their use for screening in the general population. In addition, evidence supporting the clinical utility of multi-component models was also identified during the searches, suggesting that aggregation of multiple health indicators into a model provides a more robust method of determining individual risk. Tests where clinical utility was not supported focussed mainly on prostate and lung cancer, however all were considered to still be under investigation and further research and development was needed to establish their clinical utility.

The broader search examining the clinical utility of genetic testing in cancer prevention correlated with our results on the clinical utility of specific tests. The clinical utility of high-risk familial variants has been established and these tests are in use in their intended populations combined with additional features such as genetic counselling. The search considering PRS identified guidelines regarding breast, liver, and prostate cancer, however the routine use of PRS is not currently recommended.

CVD: Of the 775 papers identified in the scoping review, 24 were selected for further analysis, from which we identified 59 test definitions utilising 33 unique biomarkers. They covered a wide range of conditions including coronary artery disease (CAD), atrial fibrillation, abdominal aortic aneurysms, and ischemic stroke, which was the most frequent condition addressed. Eight tests had evidence supporting their clinical utility. Four of these covered two multi-component models, one of which screened for atrial fibrillation in different populations and one which identified patients at risk of myocardial infarction (MI) and stroke later in life. The remaining four tests with evidence supporting clinical utility also employed existing validated methods, namely coronary artery calcium score and apolipoprotein A

PROPHET
a PeRsOnalized Prevention roadmap for the future HEalThcare
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assessments to identify risk of CVD. As seen in cancer, the tests incorporate previously validated health markers to enhance the utility of existing methods. However, most tests had no evidence identified – supportive or not supportive – of clinical utility. This was particularly the case for genetic markers associated with CVD where we did not identify any evidence of clinical utility.

The broader genetic search demonstrated that genetic testing in CVD is currently established in people with high-risk variants, strong family histories or those already diagnosed with CVD with a known genetic basis. In other CVD conditions routine genetic testing is not recommended. In terms of PRS the current guidelines and documents identified that they have potential in improving risk assessment along with guiding therapeutic options. However, the methodology is still in the developmental stages and is not yet recommended for routine implementation.

Neurodegenerative diseases: Of the 286 papers identified in the scoping review ten were selected for further analysis, from which 32 tests were defined utilising 25 unique biomarkers. The majority of these tests focussed on Alzheimer's disease (AD) followed by Parkinson's disease (PD) and multiple sclerosis (MS). One test, which used structural magnetic resonance imaging (sMRI) to determine the risk of AD in patients with subjective cognitive decline, had evidence showing clinical utility was not supported. The remaining tests had no evidence identified either supporting or refuting their clinical utility. Most tests consisted of biochemical biomarkers or utilised imaging techniques which are already well established in the diagnosis and monitoring of neurodegenerative diseases, rather than for prevention. Whilst many of the neurodegenerative diseases investigated are thought to have genetic causes, for example approximately 25% of AD cases are estimated to be familial, we identified only five tests based on genetic biomarkers, none of which had any evidence regarding clinical utility. At this stage personalised prevention for neurodegenerative diseases appears to remain in the research and development arena.

Conclusions: Determining the clinical utility of a biomarker and its use as a test can be challenging, not least due to the variation in definitions of clinical utility and how it can be determined. We did not identify a suitable method for determining the evidence of clinical utility of the tests involving the biomarkers from Task 2.1.1. We therefore developed a disease agnostic framework that can be used to identify evidence regarding the clinical utility of a test. By using multiple sources in the search we have achieved a comprehensive assessment of available evidence. The search strategy is flexible depending on what evidence is required and can be used for other disease groups.

Our results demonstrate significant gaps between the early association of a biomarker with a disease process and its implementation as a test in personalised prevention. In each disease group most tests did not have any evidence identified regarding their clinical utility. Genetic biomarkers featured prominently in each disease group, and we performed broader searches considering genetic testing, however very little evidence was identified regarding their clinical utility, unless they were already in use in hereditary cancer testing. Our results demonstrate significant evidence gaps and lack of translation of promising biomarkers for prevention. This requires urgent attention in order to accelerate the development of improved prevention interventions and programmes for the European population.

PROPHET
a PeRsOnalized Prevention roadmap for the future HEalThcare
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Recommendations for the research agenda for prevention:

Based on our findings and analyses, we recommend the following actions for improving research efforts in the area of personalised prevention:

1. Research funders should continue to fund high quality biomarker research and the necessary translation and implementation studies for biomarkers and the tests in which they are used.
2. Research funders should encourage the evaluation and validation of biomarkers and the tests in different subpopulations (i.e., age groups; gender; population group) to improve information for personalised prevention approaches.
3. Research funders should consider developing and implementing a prioritisation approach to support the necessary implementation and translation research for biomarkers/tests for prevention purposes.
4. Researchers in the field of biomarkers should ensure that their research clearly contributes to a test definition for further translational research and prevention purposes.
5. Research activity should continue to identify biomarkers in areas such as genomics, epigenomics, proteomics, metabolomics, microbiomics and exposomics, integrating this information to enhance their usefulness for personalised prevention in terms of the development of risk prediction models.
6. Research in the use of machine learning algorithms should be supported as this can improve biomarker validation efforts and the development of risk prediction models. However, standardisation in research methods and reporting, is needed to translate these results into clinical practice.
7. Greater efforts and resources are needed to integrate electronic health records (EHRs) into research, for example risk modelling using large-scale omics datasets linked with EHRs and other sources of data including socio-demographic and environmental exposures. Appropriate research study designs incorporating these elements will be needed to improve preventive strategies.
8. Research funders should also promote the consideration of other domains (e.g. social, behavioural, environmental) to allow a more complete perspective of the usefulness of any proposed test or biomarker in terms of personalised prevention from the public health perspective.

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1 Introduction

1.1 Background

The concept of personalised medicine is being increasingly discussed within the context of health system strategy and delivery of care. Developments in technology, and healthcare innovation more broadly, have enabled the ability to analyse, process and combine unprecedented sources and quantities of data e.g. environmental, clinical, socio-demographic, epidemiological and biological. This has not only supported understanding of the origin and evolution of chronic diseases, but has also led to the development of more targeted strategies to prevent, detect or treat disease.

According to the European Council *Conclusion on personalised medicine for patients* (2015/C421/03), the term personalised medicine defines a medical model that involves characterising the genotypes, phenotypes, lifestyle and environmental exposures of individuals in order to tailor the right therapeutic strategy for the right person at the right time, and/or to determine disease predisposition and/or to provide timely and targeted prevention [1]. From the point of view of public health, personalised prevention is an important concept within this model. Personalised prevention aims to prevent the onset, progression and recurrence of disease by the adoption of targeted and timely interventions that consider biological information (e.g. genetics and other biomarkers, other health conditions), demographics, environmental and behavioural characteristics, and the socio-economic and cultural context of individuals [1, 2]. Implementing personalised prevention approaches at a population level could prevent patients becoming ill or support early diagnosis in time to prevent disease progression, improve health, and increase healthy life span.

Non-communicable diseases (NCDs) are a prime target for personalised prevention due to their rising incidence, mortality, and impact in terms of disability-adjusted life years [3-6]. According to the World Health Organization, each year NCDs kill 41 million people, equivalent to 74% of all deaths globally [7]. Within the EU, NCDs may account for 80% of the overall burden of disease and, in 2021, one third of EU adults were reported to be suffering from a chronic condition [8]. The two main causes of NCD-related mortality in the EU in 2019 were circulatory diseases, which accounted for over 1.6 million deaths (35% of all deaths), and cancer, which accounted for almost 1.2 million deaths (26% of all deaths) [8]. Neurodegenerative diseases, including dementia, are also a significant contributor to NCD-related morbidity, mortality and disability — ranking third, according to some authors [9] — and a growing cause for concern in ageing societies.

Therefore, in 2019, the *Personalised medicine for disease prevention* (PRECeDI) consortium recommended the identification of biomarkers that could be used in NCD prevention. A biomarker is understood to be a substance, structure, characteristic or process that can be objectively measured as an indicator of normal biological processes, pathogenic processes or biological responses to a therapeutic intervention or exposure [10, 11]. An appropriate biomarker could be identified by stratifying populations by disease risk, or by guiding primary, secondary and tertiary preventive interventions [12]. Biomarkers identified this way

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could further support the development of personalised medicine approaches by more precisely highlighting which individuals can benefit from specific preventive strategies or by informing how to better design and adapt therapies for specific patients or groups of patients [13].

1.2 Context – D2.1: personalised prevention biomarkers

The "PeRsOnalised Prevention roadmap for the future HEalThcare" (PROPHET) project, funded by the European Union's Horizon Europe research and innovation programme and linked to ICPerMed, seeks to assess the effectiveness, clinical utility, key success factors and existing gaps in current personalised preventive approaches, as well as their potential to be implemented in healthcare settings. It also aims to develop a Strategic Research and Innovation Agenda (SRIA) for the European Union. Work package 2 of the PROPHET project brings together a range of approaches, from scientific to social and legal research, which are essential for the SRIA to be anchored in the existing personalised prevention landscape.

In task 2.1.1, we carried out a scoping review of the current research landscape of biomarkers for primary or secondary personalised prevention in the general adult population for cancer, cardiovascular (CVD) and neurodegenerative diseases. The following conditions were evaluated for each disease:

- **Cancer:** We selected the malignant neoplasms with the greatest mortality and incidence rates in Europe. According to the European Cancer Information System these are breast, prostate, colorectal, lung, bladder, pancreas, liver, stomach, kidney, and corpus uteri neoplasms [14]. Additionally, cervix uteri and liver cancers were also included due to the existence of public health preventive programs (i.e. vaccination, screening) [15, 16].
- **Cardiovascular diseases:** We included the following diseases, which are among the main causes of CVD death: ischemic heart disease (49.2% of all CVD deaths), stroke (35.2%) (this includes ischemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage), hypertensive heart disease (6.2%), cardiomyopathy and myocarditis (1.8%), atrial fibrillation and flutter (1.7%), non-rheumatic valvular heart disease (0.9%), aortic aneurysm (0.9%) and peripheral artery disease (0.4%) [6]. Of note, those CVDs of infectious aetiology (i.e. rheumatic heart disease or endocarditis) were not considered. Arterial hypertension is a risk factor for many cardiovascular diseases and for the purposes of the review was considered as an intermediary disease that leads to CVD.
- **Neurodegenerative diseases:** We included the leading non-communicable neurodegenerative causes of death, which are Alzheimer's disease or other dementias (20%), Parkinson's disease (2.5%), and multiple sclerosis (0.2%) [3]. Alzheimer's disease, vascular dementia, frontotemporal dementia, and Lewy body disease were specifically searched for, following the pattern of European dementia prevalence studies [17]. Additionally, amyotrophic lateral sclerosis, the most common motor neuron disease was included [3, 18].

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a PeRsOnalized Prevention roadmap for the future HEalThcare
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Full details of this review are available in D2.1. In summary, three rapid scoping reviews were carried out in parallel, one for each disease. A standard protocol was designed for the scoping review process which was then adapted to each specific condition. The review focussed on publications in English released between 2020 and 2023. Publications were screened first based on their title and abstract and then by full text. Data was extracted from the publications that progressed through the full screening process.

The results showed that the most prolific field of biomarker research for primary or secondary prevention is cancer, followed by CVD, then neurodegenerative diseases. The following biomarker categories were included:

- **Molecular biomarkers**: Biological molecules, e.g. DNA, RNA, proteins, or metabolites, measured in bodily fluids
- **Cellular biomarkers**: Cytological and histological biomarkers identified from cells/cellular components and measured using techniques such as staining, immunohistochemistry or *in situ* hybridisation
- **Physiological biomarkers**: Indicators of functional changes in the body e.g. blood pressure, heart rate, patterns of movement.
- **Imaging biomarkers**: Features identified in medical images generated using techniques, e.g. X-rays, magnetic resonance imaging (MRI), positron emission tomography (PET), computed tomography (CT) scans, that help visualise and measure structural, functional, or molecular changes in organs or tissues.
- **Anthropometric biomarkers**: Indicators of physical characteristics of the body e.g. body mass index (BMI), waist circumferences, body fat percentage.

Key findings were:

- **Cancer**. Of the 11,266 articles found, 843 met the inclusion criteria. Primary prevention research was mainly focused on molecular biomarkers (mostly genetic), while imaging biomarkers were more prominently studied in the context of secondary prevention. There was limited research on biomarkers for primary/secondary prevention of corpus uteri, bladder, and kidney cancer compared to other types of cancer.
- **CVD**. Of the 5,288 articles found, 775 met the inclusion criteria. Molecular biomarkers, especially in ischemic heart disease (IHD) and stroke, the leading causes of CVD death, were the most commonly researched. In primary prevention, most research activity was for IHD and stroke within general and high-risk CVD populations (for example, patients diagnosed with chronic kidney disease were considered to be high-risk for CVD) and for the molecular/genomics and imaging biomarker categories. In secondary prevention, most research activity was in IHD and stroke within general and high-risk CVD populations and for the molecular/biochemistry (biochemical) and imaging biomarker categories.
- **Neurodegenerative diseases**. Of the 2,014 articles found, 286 met the inclusion criteria. The most notable finding is the considerable focus on Alzheimer's disease. In contrast, there was a scarcity of available research for other neurodegenerative diseases, specifically Lewy body disease and frontotemporal dementia. The research on Alzheimer's disease was primarily for secondary prevention strategies, whilst for

PROPHET
a PeRsOnalized Prevention roadmap for the future HEalThcare
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the other diseases the focus was on primary prevention. Molecular biomarkers were a major focus of the research in neurodegenerative diseases, followed by imaging biomarkers.

Across all three disease groups, findings were that:

- Most research activity is on molecular biomarkers
- Imaging biomarkers are the second most common group investigated, except for cancer where anthropometrics measures are more commonly explored – mostly BMI
- Imaging biomarkers are more common in secondary prevention, particularly in neurodegenerative diseases
- Cellular biomarkers were mostly limited to cancer studies
- Physiological biomarkers were more common in secondary prevention of CVD than other diseases
- Molecular biomarkers – genetic/genomic – were extensively studied for primary prevention and ranked second in those identified for secondary prevention.
- The use of digital technologies with new biomarkers was identified, with a focus on the use of artificial intelligence including machine learning. Its application was primarily limited to predictive models or early detection in studies utilising molecular and imaging techniques (e.g. radiomics).

1.3 Aim of this report – clinical utility

The aim of Task 2.1.2 is to undertake further analysis and research to establish the level of evidence for clinical utility for personalised prevention of the biomarkers identified in Task 2.1.1 and outlined in D2.1.

For the purposes of the PROPHET research programme, consortium partners have agreed the following definition of clinical utility:

Clinical utility of a test refers to the likelihood that it provides information that is of value to the person being tested to identify if an effective intervention or preventive strategy is required

Determining clinical utility of a biomarker is a complex process. The spectrum of clinical utility considered under different evaluation frameworks varies. Few evaluation frameworks define the level of evidence required for clinical utility to be satisfied. Different decisions may be reached with respect to clinical utility based on the evidence considered, the nature of the decision-making process and those involved. Thorough assessment and evaluation of existing research to determine potential clinical utility of a test is done by experts with knowledge about the disease, the clinical applications of testing and clinical care pathways, as well as a number of other factors (Figure 1).

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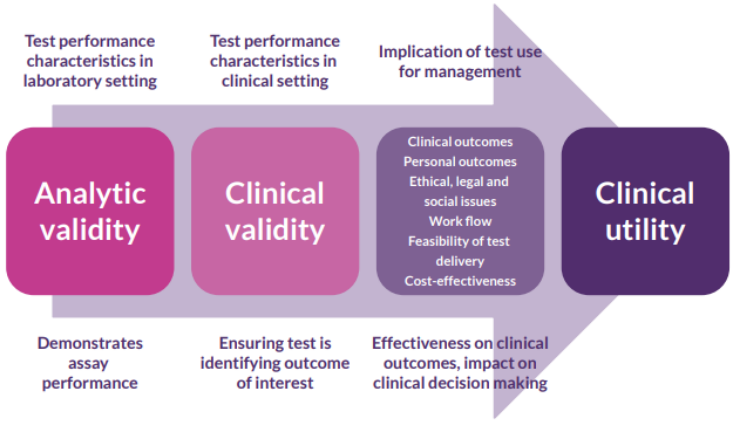
Figure 1. Overview of the processes that can ultimately lead to demonstration of clinical utility [19].



The clinical utility of different aspects of clinical care such as a diagnostic test or biomarker for early detection can vary depending upon multiple factors including the context of use, disease of interest, cost of the test and its ease of use [19, 20]. A systematic strategy to evaluate the clinical utility of tests involving novel assays and biomarkers is therefore a highly complex undertaking and there is no standard approach.

To allow for the assessment of the clinical utility of tests incorporating the relevant biomarkers identified in task 2.1.1, a methodology was developed which is outlined in the next section. A key principle of our methodology is that the authors and institutions developing guidelines make some form of assessment of clinical utility of the interventions and tests considered as part of these guidelines. Whilst we describe the results of our searches, we do not appraise nor assess the nature and quality of the relevant guideline development process.

To enable this, we first defined the clinical test in which the biomarker could be used as described in the associated publication i.e., the 'test definition'. This allowed us to examine evidence for clinical utility specific to the disease, population and purpose in which the biomarker is intended to be used [21]. The strategy enables users to search for high quality information such as national and international guidelines, health technology assessments (HTAs) and cost effectiveness assessments (CEAs) to identify supporting evidence for the clinical utility of a test using a specific biomarker.

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2 Methods

2.1 Biomarker selection

A master list of biomarkers was constructed using the results from Task 2.1.1. This list was substantial, and many of the biomarkers covered were being studied primarily as part of basic science research projects.

Any assessment of clinical utility requires a certain level of scientific evidence across different domains as shown in Figure 1. In order to focus our research efforts, we opted to create a prioritised biomarker list. Biomarkers identified in Task 2.1.1 were prioritised first based on the study design of the original papers: systematic reviews with meta-analyses, randomised control trials or from a review (including systematic, scoping, and umbrella reviews). These study designs offer a higher level of evidence than those generated from, for example, a single case-control study design. This follows the principles of the evidence-based medicine 'pyramid of evidence' [22]. The prioritised biomarkers list was used for further assessment of clinical utility. The master list of biomarkers is available from the authors on request.

2.2 Defining the test

For a biomarker to have clinical utility, it must be incorporated into a test. We created test definitions for each biomarker in the prioritised list. A test definition describes HOW an assay detects [21]:

- A biomarker
- For a particular disease (WHAT)
- In a particular population (WHO)
- For a particular purpose (WHY)

The test was defined based on information from the paper that identified the biomarker. If the biomarker's test definition was not clearly described in the paper, then it was excluded. In addition, if the paper indicated that there was no association between the biomarker and the disease of interest, it was excluded.

2.3 Searches

The purpose of these searches was to identify and provide an overview of available evidence and the general recommendations available around the use of a particular test.

We gathered evidence from either guidelines or HTA and CEAs. We considered guidelines to be the highest level of evidence since clinical utility assessment is an integral part of the process of guideline development. In contrast, HTAs and CEAs provide key assessment of potential clinical utility. The resources used to search for guidelines, HTA and CEAs were:

PROPHET
a PeRsOnalized Prevention roadmap for the future HEalThcare
Funded by the European Union

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- Guidelines
  - Guideline central [23]
  - TRIP [24]: Turning Research into Practice (has guidelines, HTAs and CEAs)
- HTA
  - International HTA database [25]
  - CRD Database [26](also does CEA search)
  - TRIP database (has guidelines, HTAs and CEAs)
- Cost effectiveness analysis studies
  - CEA registry [27]
  - CRD Database (also does HTA search)
  - TRIP database (has guidelines, HTAs and CEAs)

Guideline Central is an open access repository of evidence-based guidelines to provide quick reference to decision making tools for clinicians, however it is more limited in the resources available. The TRIP database is a clinical search engine that provides access to evidence based documentation including guidelines, RCT data, systematic reviews and primary research articles. Basic access to TRIP is free however to utilise the full functionality a subscription to TRIP Pro is required. TRIP provides additional features including an internal appraisal of the quality of evidence, such as a TRIP score (see below) in the case of guidelines. The International HTA database collates health technology assessment data from global sources and is operated by The International Network of Agencies for Health Technology Assessment. The Centre for Reviews and Dissemination (CRD) database provides access to systematic reviews and economic evaluations of health and social care interventions and summaries of Cochrane systematic reviews and protocols. The Cost-Effectiveness Analysis (CEA) Registry is a database containing cost-utility analyses on a wide range of diseases and treatments. It is operated by the Center for the Evaluation of Value and Risk in Health.

These databases use the same search strategy as many other literature search databases, for example the US National Institutes of Health PubMed database. The TRIP database has recently released the option to carry out searches using Boolean operators, increasing search efficiency.

Search terms included the disease of interest, the purpose (i.e., prevention) and the biomarker name. Other features in the test definition, for example a specific population such as diabetics, or a specific age range or gender, were used to inform the searches when needed. For genetic biomarkers the searches were focused on gene names in which the specific genetic mutations or single nucleotide polymorphisms (SNP) reported in the papers were located.

Search results were listed and reviewed from the most recent to the oldest until up to four items of evidence were collected following the criteria described below:

- As guidelines were considered to be the highest level of evidence, no further searches were done if a guideline was found.
- If there were no guidelines, then searches for HTAs and CEAs were done and the results were considered together to assess clinical utility.

PROPHET
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Results from these searches were considered to be evidence where they corresponded to the test definition (e.g. the guideline addressed the use of the test in the specified disease, population and given purpose). The clinical utility assessment could result in the biomarker-based test being recommended for use, not recommended for use either as there was limited utility, or that further demonstration of its utility was still needed and not currently recommended for use.

The production of guidelines is a complex task and there are a multitude of available methods, some more rigorous than others. To help users assess guideline quality, in some cases TRIP provides a guideline score which relies on the following five criteria [28]:

1. Has the methodology been published?
2. Has the evidence been graded according to the international GRADE system?
3. Have searches for systematic evidence been undertaken?
4. Is there clarity about funding?
5. Is there any conflict of interest.

Higher TRIP scores indicate a stronger evidence base for the guideline. The associated TRIP scores for the guidelines were noted when available. A full search workflow is available from the authors on request.

2.4 Information captured from the searches

An individual report, following a standard template, was created for each biomarker-based test based on the results of the searches conducted. This report includes context for the biomarker's use, the test definition, the search terms used for each database, the findings of the search including references to any evidence, and a conclusion summarising the findings. In some cases, a biomarker might have different tests (i.e. different population or different biological sample).

In guidelines, the test using the biomarker of interest must be included to be considered as evidence for this review. Similarly, for HTAs and CEAs, the test would be the focus of the assessment. Only documents that discuss a test were considered. Documents that concluded a biomarker may have potential, but did not go into more detail, were not included.

An individual report for each test definition was produced based on the results of the searches carried out. Where the test definition has multiple populations or diseases of interest a report combining them together was produced. Reports for each biomarker-based test with evidence are available in Section 3 (Results), reports for tests with no evidence are available from the authors on request.

2.5 Search methodology for genetic tests

In the scoping review from Task 2.1.1, a large number of genetic biomarkers were identified for personalised prevention, demonstrating considerable research in this field. In order to obtain a broader understanding of the clinical relevance of genetic biomarkers in prevention, these biomarkers were evaluated as a group using the same methodology as outlined above.

The search terms used were "genetic testing", "germline testing" or "genotyping" followed by "prevention", "preventive" or "screening".

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2.6 Search methodology for polygenic scores

Polygenic scores (PGS) are considered novel, promising biomarkers for personalised prevention, particularly in the context of complex diseases. They can be included in multivariate risk prediction models which include lifestyle factors or other biomarkers.

These scores effectively combine and summarise disease-associated genetic variants known as single nucleotide polymorphisms (SNPs), to determine an individual's genetic predisposition to a disease, which can in turn could inform personalised prevention strategies. Therefore, an additional search for evidence of clinical utility focused on the use of PGS in prevention was conducted. The search term “polygenic score” was used, followed by “prevention”, “preventive” or “screening” and the specific disease. Given that the term polygenic risk score (PRS) is commonly used in the results returned, we have used this term in the remainder of this report.

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3 Results

3.1 Cancer

For cancer, as outlined in **Table 3.1A**, from the 843 papers that were examined in Task 2.1.1 , 57 corresponded to the articles with the highest level of evidence, including 40 systematic reviews with meta-analyses, 11 reviews and 6 randomised-controlled trials (RCT). The biomarkers from these papers formed the prioritised biomarker list for Task 2.1.2.

Table 3.1A. Cancer papers from Task 2.1.1 prioritised for Task 2.1.2 by study type.

Total number of papers identified in the scoping review	843
Systematic review + Meta-analysis papers	40
Review papers	11
RCT papers	6
Prioritised papers for review	**57**

3.1.1 Development of test definitions in cancer

Test definitions were developed for the various biomarkers which resulted in 115 individual test definitions comprising 62 unique biomarkers. Thirteen papers and their respective biomarkers were excluded due to lack of association biomarker/outcome or to inability to create a test definition with the data provided in the paper. The majority of the biomarkers focused on breast, prostate, liver and gastric cancers, followed by colorectal, lung, pancreatic, and cervical cancer. Thirty-three of the biomarkers included a genetic marker, either alone or included within a more complex model.

We found evidence for 22 of the 62 biomarkers, of which 15 indicated that the test evaluated had clinical utility (section 3.1.2) and seven for which no clinical utility was described in the reports found (section 3.1.3). For the rest of the biomarkers, no guidelines, HTA or CEA documents were identified that matched the test definition.

3.1.2 Tests with evidence of clinical utility – cancer

Following the searches, 14 reports for the tests were produced that had evidence of clinical utility. The 14 reports covered 15 biomarkers and 15 tests (Table 3.1B).

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TABLE 3.1B. Tests for cancer with evidence regarding their clinical utility, including biomarker details. Matching shaded rows and paper references included to indicate test definitions derived from the same paper.

Test	Biomarker
Evidence supporting the clinical utility of the biomarker	
Use of the combination of digital breast tomosynthesis (DBT), two-dimensional mammography (2DM) and breast density assessment to improve the screening of **breast cancer** in the general female population.	Breast density combined with Digital Breast Tomosynthesis (DBT) and two-dimensional mammography (2DM). Moshina N, Aase HS, Danielsen AS, et al. *Radiology*. 2020;297(3):522-531. doi:10.1148/radiol.2020201150
Genetic test to identify: 1. *BRCA1* mutations in males to identify increased risk of **prostate cancer** (**PCa**) OR 2. *BRCA2* mutations in males to identify increased risk of **PCa**.	*BRCA1* and/or *BRCA2* genes. Marino F, Totaro A, Gandi C, et al. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3
Genetic test to identify mutations in the *CHEK2* gene indicating an increased risk of fatal **PCa**.	*CHEK2* gene. Marino F, Totaro A, Gandi C, et al. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3
The GALAD score - a serum biomarker-based model that includes 5 variables (gender, age, AFP-L3, AFP and DCP) to predict the probability of having **liver cancer** among patients with chronic liver disease	GALAD score. Guan MC, Zhang SY, Ding Q, et al. JCM. 2023;12(3):949. doi:10.3390/jcm12030949
Genetic test for the *GREM1* gene to identify the risk of **CRC** in the general population.	*GREM1* gene. Hajibabaie F, Abedpoor N, Assareh N, et al. JPM. 2022;12(3):456. doi:10.3390/jpm12030456
Genetic test for the *HOXB13* gene to provide the risk of **PCa**.	Homeobox 13 (*HOXB13)* gene. Marino F, Totaro A, Gandi C, et al. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3
Genetic test for the *MLH1* gene to provide the risk of **PCa**.	*MLH1* gene. Marino F, Totaro A, Gandi C, et al. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3
Genetic test for the *MSH2* gene to provide risk of **PCa**.	*MSH2* gene. Marino F, Totaro A, Gandi C, et al. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3
Genetic test for the *MSH6* gene to provide the risk of **PCa**.	*MSH6* gene. Marino F, Totaro A, Gandi C, et al. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3
Genetic test for the *PALB2* gene to provide the risk of **PCa**.	*PALB2* gene. Marino F, Totaro A, Gandi C, et al. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3

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Genetic test for the *PMS2* gene to provide the risk of **PCa**.	*PMS2* gene. Marino F, Totaro A, Gandi C, et al. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3
Genetic test for the *MLH3* gene to provide the risk of **colorectal cancer (CRC)** in the general population.	*MLH3* gene. Hajibabaie F, Abedpoor N, Assareh N, et al. JPM. 2022;12(3):456. doi:10.3390/jpm12030456
Stockholm3 is a blood-based diagnostic test to predict risk of **prostate cancer** in men aged 45 to 74 years with PSA of at least 1.5 ng/ml and no previous prostate cancer diagnosis	Stockholm3 test. Nordström T, Discacciati A, Bergman M, et al. Lancet Oncol. 2021;22(9):1240-1249. doi:10.1016/S1470-2045(21)00348-X
The Tyrer-Cuzick model is a statistical tool that estimates an individual's risk of having breast cancer high risk mutations, and, therefore, the risk of developing **breast cancer** in the general adult female population	Tyrer-Cuzick model. Vilmun BM, Vejborg I, Lynge E, et al. Eur J Radiol. 2020;127:109019. doi:10.1016/j.ejrad.2020.109019
ExoDx Prostate IntelliScore (EPI) for improved screening of **prostate cancer** in men 50 years or older with a PSA between 2-10 ng/ml.	ExoDx Prostate IntelliScore test (EPI test). Tutrone R, Donovan MJ, Torkler P, et al. Prostate Cancer Prostatic Dis. 2020;23(4):607-614. doi:10.1038/s41391-020-0237-z
LCDRAT prediction model to identify patients at high risk of **lung cancer** death in adults for LDCT screening.	Lung Cancer Death Risk Assessment Tool (LCDRAT) prediction model. Toumazis I, Bastani M, Han SS, Plevritis SK. Lung Cancer. 2020;147:154-186. doi:10.1016/j.lungcan.2020.07.007
Michigan Prostate Score to estimate individual's risk of developing **prostate cancer.**	The Michigan Prostate Score (MiPS). Wang L, He W, Shi G, et al. *Front Oncol.* 2022;12:1048876. doi:10.3389/fonc.2022.1048876
PanCan prediction model to estimate the probability of **lung cancer** for screen-detected solidary pulmonary nodules in adult patients.	Pan-Canadian Early Detection of Lung Cancer Study (PanCan) prediction model . Toumazis I, Bastani M, Han SS, Plevritis SK. Lung Cancer. 2020;147:154-186. doi:10.1016/j.lungcan.2020.07.007
PLCOm2012 model to identify patients at high risk of **lung cancer** in ever-smoker adults for LDCT screening.	Revised Prostate, Lung, Colorectal, and Ovarian (PLCO) model for ever smokers made applicable to the National Lung Screening Trial (NLST) data (PLCOm2012) prediction model. Toumazis I, Bastani M, Han SS, Plevritis SK. Lung Cancer. 2020;147:154-186. doi:10.1016/j.lungcan.2020.07.007
Prostate Health Index (a combination of total PSA, free PSA and p2PSA measured in serum) for the improved screening of **prostate cancer** in the general male population.	Prostate Health Index (PHI). Agnello L, Vidali M, Giglio RV, et al. Clin Chem Lab Med. 2022;60(8):1261-1277. doi:10.1515/cclm-2022-0354
SelectMDX is a urine test that measures the expression of two mRNA cancer-related biomarkers and combines them with clinical risk factors (age, PSA, prostate volume, family	SelectMDx. Wang L, He W, Shi G, et al. Front Oncol. 2022;12:1048876. doi:10.3389/fonc.2022.1048876

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history, digital rectal exam) to determine the risk of developing clinically **significant prostate cancer** in men.	

The tests with evidence often used multi-component models that included several biochemical or physiological biomarkers in addition to personal health data. Thus, guidelines were identified supporting the use of the Tyrer-Cuzick model, GALAD score and Stockholm3 test to predict the individual risk of developing breast cancer, liver cancer and prostate cancer (PCa), respectively. This suggests that the use of multi-factorial tools for primary and secondary prevention provide a more robust assessment of individual risk.

This is also reflected in the test focussing on screening of breast cancer in the general female population including the assessment of breast density to improve the usefulness of digital breast tomosynthesis (DBT) combined to two-dimensional mammography (2DM). For this test, we were not able to find any guidelines, but we identified one HTA and one CEA which provided some evidence of clinical utility.

Furthermore, we identified a number of genes linked to familial cancer in two papers. One focussed on PCa and resulted in nine tests. These tests considered known genes with pathogenic variants with moderate to high penetrance such as *BRCA1*, *BRCA2*, *CHEK2* and *HOXB13*. We found evidence recommending their use; however, this evidence only considered the genes as part of multi-gene panel tests, not in isolation, for individual risk assessment and stratification among high risk individuals (i.e., those with family history of PCa or in whom a genetic syndrome is suspected).

The same observation was made in the tests with evidence supporting clinical utility for colorectal cancer.

There were seven tests with evidence but no proven clinical utility, of which five included models, scores, and tests. These sought to estimate the risk or to improve the screening of certain types of cancer, by combining biomarkers with age, sex or other individual features, sometimes complemented by other clinical data or family history of the tumour.

Among them, PCa was the one that was most represented. Michigan Prostate Score (MiPS), the ExoDx Prostate IntelliScore test (EPI test) and the SelectMDx are scores that include different serum and/or blood biomarkers alongside other variables to improve the identification of clinically relevant tumours in the screening of PCa. Currently, the evidence suggests that, even though these three tests are promising, they need further analysis and validation before including them in clinical settings. In addition, the Prostate Health Index (PHI) aims to improve the limitations of PSA-based screening of PCa by measuring three forms of PSA and combining them into a single score. However, evidence highlights that, although it may improve the prediction of PCa, at the time of evaluation it was not cost-effective and requires further validation.

We also found several predictive models that estimate the risk of developing lung cancer (LCDRAT, PLCOm2012 and Pancan) intended to inform lung cancer screening programs using low dose computed tomography (LDCT). The retrieved guideline, issued in 2013, did not show clear recommendations regarding the clinical utility of these tests and underlines that

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further research and data are needed to determine its clinical utility. Nevertheless, the promotion of this screening in recent years and the active research in this field should result in updated recommendations for this prevention strategy.

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Breast density combined with Digital Breast Tomosynthesis (DBT) and two-dimensional mammography (2DM)

Biomarker name: Breast density combined with Digital Breast Tomosynthesis (DBT) and two-dimensional mammography (2DM) [A].

Biomarker context: Breast density is a known risk factor for breast cancer classically measured in breast mammograms either by trained radiologists, sometimes helped with semiautomatic software (i.e. CUMULUS) or through automatic software (i.e. VOLPARA or QUANTRA). It refers to the proportion of fibrous and glandular tissue (white) in comparison with the quantity of fatty tissue (black in the mammogram) in woman´s breasts. Many researchers are trying to improve breast cancer screening programs by including this image biomarker. Although mammography is considered the most effective method of screening for breast cancer, many cases are not detected by standard screening. Digital breast tomosynthesis (DBT) is a newly developed three-dimensional (3D) imaging technique that has the potential to improve the accuracy of mammography, as it differentiates between malignant and non-malignant features and could decrease the number of false positive recalls. Current recommendations indicate that DBT should be used in conjunction with two-dimensional (2D) mammography. Breast density might help to select those women that could benefit the most of this combination.

Test definition: Use of the combination of digital Breast Tomosynthesis (DBT), two-dimensional mammography (2DM) and breast density assessment to improve the screening of breast cancer in the general female population.

Results of the search:

No evidence was available in the form of guidelines. We were able to find one health technology assessment (HTA) and two cost effectiveness evaluations (CEA) for this test definition.

The search terms used for this biomarker´s clinical utility produced four results in Guideline Central and fifteen results in TRIP, none of which matched the test definition.

In terms of HTA and CEA documents, five results were retrieved from TRIP**,** but none focused on the disease of interest, prevention level or type of document (HTA or CEA). We were not able to generate any valid results from CRD. The International HTA database search yielded twelve results with one matching the test definition. Two out of the four results that were retrieved from CEA initially matched the test definition, one of them did not consider breast density in its assessments and has been excluded.

Evidence of clinical utility for the test:

Evidence 1: TOMMY trial: A comparison of TOMosynthesis with digital MammographY in the UK NHS Breast Screening Programme [B].

The document was published in January 2015 by the National Institute for Health Research (NIHR) at the Health Technology Assessment Journal. The original country of publication is the United Kingdom.

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The objective of this document was to assess the diagnostic accuracy of DBT in conjunction with two-dimensional (2D) mammography or synthetic 2D mammography, against standard 2D mammography and to determine if DBT improves the accuracy of detection of different types of lesions. Breast density was assessed with Quantra and Volpara softwares. Its analysis shows a small improvement in breast cancer detection rates but a clear improvement in the specificity when DBT is used in conjunction with 2D images or synthetic images compared with 2D alone across all age groups and breast densities, particularly for women aged 50–59 years and for breast density ≥ 50%. While highlighting the need for further validation for the implementation in clinical settings, it also remarks that randomised control trials could imply a delay in the implementation of this key imaging technology in screening by 5–7 years.

Evidence 2: Comparative effectiveness of combined Digital Mammography and Tomosynthesis screening for Women with Dense Breasts [C].

The document was published in October 2014 by the National Institutes of Health Research at the Radiology Journal. The original country of publication is the United States of America.

The objective of this document was to evaluate the effectiveness of combined biennial digital mammography and tomosynthesis screening, compared with biennial digital mammography screening alone, together with radiologist breast density assessment (BIRADS). This analysis indicates that adding tomosynthesis to biennial digital mammography screening for women aged 50–74 years with dense breasts is likely to improve health outcomes at a reasonable cost relative to biennial mammography screening alone.

Conclusion: The only HTA and CEA documents identified in the searches were from almost a decade ago. They are however supportive of the use of combined digital breast tomosynthesis and digital mammography in combination with breast density to improve the screening of breast cancer in the general female population.

Guideline Central search terms used: digital breast tomosynthesis; two-dimensional synthetic mammography

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: ("breast cancer" AND ("digital breast tomosynthesis" OR "two dimensional synthetic mammography") AND ("prevent" OR "screen" OR "early diagnos")) from_date:2013

HTA search terms for TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: ("breast cancer" AND ("digital breast tomosynthesis" OR "two dimensional synthetic mammography") AND ("prevent" OR "screen" OR "early diagnos" OR "health technology assessment" OR "economic evaluat" OR "cost effective")) from_date:2013

Search terms used in CRD database: digital breast tomosynthesis; two-dimensional synthetic mammography

HTA search terms used in International HTA database: digital breast tomosynthesis; two-dimensional synthetic mammography

CEA search terms used in CEA registry: digital breast tomosynthesis; two-dimensional synthetic mammography

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A. Moshina N, Aase HS, Danielsen AS, et al. Comparing Screening Outcomes for Digital Breast Tomosynthesis and Digital Mammography by Automated Breast Density in a Randomized Controlled Trial: Results from the To-Be Trial. *Radiology*. 2020;297(3):522-531. doi:10.1148/radiol.2020201150

B. Gilbert FJ, Tucker L, Gillan MG, et al. The TOMMY trial: a comparison of TOMosynthesis with digital MammographY in the UK NHS Breast Screening Programme – a multicentre retrospective reading study comparing the diagnostic performance of digital breast tomosynthesis and digital mammography with digital mammography alone. *Health Technol Assess*. 2015;19(4):1-136. doi:10.3310/hta19040

C. Lee CI, Cevik M, Alagoz O, et al. Comparative Effectiveness of Combined Digital Mammography and Tomosynthesis Screening for Women with Dense Breasts. *Radiology*. 2015;274(3):772-780. doi:10.1148/radiol.14141237

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BRCA1/ BRCA2 genes

Biomarker name: BRCA1 and/or BRCA2 genes [A].

Biomarker context: Genetic testing in prostate cancer (PCa) is becoming standard of care among those men with familial history of PCa or personal history of other tumours. It can provide key information for clinical management, as well as offering crucial insights into familial cancer risk. Identification of germline gene alterations in PCa patients provides an opportunity for cascade testing in family members, opening up avenues for cancer prevention and early diagnosis among those who may also carry the same germline gene alterations.

Test definition 1: Genetic test to identify BRCA1 variants in males to identify increased risk of PCa.

Test definition 2: Genetic test to identify BRCA2 variants in males to identify increased risk of PCa.

Results of the search: Three guidelines were identified in Guideline Central however none were related to either test definition. Ninety-five guidelines were identified using the search terms in TRIP, which reduced to 71 when only guidelines published since 2018 were considered. The majority of the results covered breast and ovarian cancers along with genetic testing after initial diagnosis. Three guidelines aimed at early detection were identified.

Evidence 1: 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer [B].

This document, with a TRIP score of 6, considers genetic testing during various stages of PCa. It recommends that people at high-risk of PCa should undergo germline testing as soon as their risk level is determined. Those considered to be at high risk included people with a positive family history of prostate or related cancer (such as breast, ovarian, colorectal, and endometrial), those with a personal history of associated cancers, those with Ashkenazi Jewish heritage and those with ductal, intraductal or cribriform pathology. The guideline recommends that both BRCA1 and BRCA2 should be included in the germline gene panel test for PCa.

Evidence 2: Hereditary Cancer Testing Eligibility Criteria: Version 3 [C].

This document is published by the Hereditary Cancer Testing Eligibility Working Group within Ontario Health Cancer Care in 2022 and has a TRIP score of 5. It serves as a companion to Ontario's standardised Hereditary Cancer Testing Gene List for genetics professionals to determine hereditary cancer testing eligibility for early diagnosis. The genes BRCA1 and BRCA2 are both recommended to be included in germline panel testing. It has a TRIP score of 5.

Evidence 3: Clinical Appropriateness Guidelines Genetic Testing for Hereditary Cancer Susceptibility [D].

This document was published in 2023 by the American organisation Carelon Health and has a TRIP score of 0. It discusses indications for hereditary testing in specific cancers. BRCA1 and BRCA2 should be tested for in patients that fit the eligibility criteria. Patients at high risk

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of hereditary breast and ovarian cancer syndromes, which in this definition included prostate cancer, should undergo genetic testing to determine their risk of developing the disease.

Conclusion: Numerous guidelines considering genetic testing in PCa were identified although the majority examined genetic testing after diagnosis and in patients with aggressive disease. Three documents in TRIP were identified that recommended the use of BRCA1 and BRCA2 in hereditary testing for the risk of PCa with the genes being tested as part of germline genetic panels rather than in isolation.

Search terms used for this biomarker

Guideline Central search terms used: BRCA1 AND prostate

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: prostate cancer

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: BRCA1 OR BRCA2

A. Marino F, Totaro A, Gandi C, et al. Germline mutations in prostate cancer: a systematic review of the evidence for personalized medicine. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3

B. Rendon RA, Selvarajah S, Wyatt AW, et al. 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer. CUAJ. 2023;17(10):314-325. doi:10.5489/cuaj.8588

C. Holliday H. Ontario Health (Cancer Care Ontario), 2022. Hereditary Cancer Testing Eligibility Criteria: Version 3

https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/70161

D. GT02-Hereditary-Cancer-Susceptibility-10-30-2022.pdf. Accessed January 18, 2024. https://providers.carelonmedicalbenefitsmanagement.com/genetictesting/wp-content/uploads/sites/15/2022/09/GT02-Hereditary-Cancer-Susceptibility-10-30-2022.pdf

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CHEK2 gene

Biomarker name: *CHEK2* gene [A].

Biomarker context: Genetic testing in prostate cancer (PCa) is becoming standard of care among those men with familial history of PCa or personal history of other tumours. It can provide key information for clinical management, as well as offering crucial insights into familial cancer risk. Identification of germline gene alterations in PCa patients provides an opportunity for cascade testing in family members, opening up avenues for cancer prevention and early diagnosis among those who may also carry the same germline gene alterations.

Test definition: A genetic test to identify a variant in the *CHEK2* gene indicating an increased risk of fatal PCa.

Results of the search: The search terms identified one guideline in Guideline Central however this was focussed on disease management after diagnosis. In TRIP 29 results were identified with the search terms, of which two were relevant to the test definition.

Evidence 1: 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer [B].

This document, with a TRIP score of 6, considers genetic testing during various stages of PCa. It recommends that people at high-risk of PCa should undergo germline testing as soon as their risk level is determined. Those considered to be at high risk included people with a positive family history of prostate or related cancer (such as breast, ovarian, colorectal and endometrial), those with a personal history of associated cancers, those with Ashkenazi Jewish heritage and those with ductal, intraductal or cribriform pathology. The guideline recommends that *CHECK2* should be included in the germline gene panel test for PCa.

Evidence 2: Hereditary Cancer Testing Eligibility Criteria: Version 3 [C].

This document is published by the Hereditary Cancer Testing Eligibility Working Group within Ontario Health Cancer Care in 2022, has a TRIP score of 5. It serves as a companion to Ontario's standardised Hereditary Cancer Testing Gene List for genetics professionals to determine hereditary cancer testing eligibility for early diagnosis. The *CHEK2* gene is recommended to be included in germline panel testing. It has a TRIP score of 5.

Conclusion: The *CHEK2* gene is one of the established genes that carry pathogenic variants that increase a carrier's risk of PCa. Both guidelines identified recommend the use of *CHEK2* as part of hereditary PCa multi-gene screening panels in individuals at high risk of PCa.

Search terms used for this biomarker

Guideline Central search terms used: CHEK2 prostate

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: prostate cancer

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: CHEK2

PROPHET
a PeRsOnalized Prevention roadmap for the future HEalThcare
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A. Marino F, Totaro A, Gandi C, et al. Germline mutations in prostate cancer: a systematic review of the evidence for personalized medicine. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3

B. Rendon RA, Selvarajah S, Wyatt AW, et al. 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer. CUAJ. 2023;17(10):314-325. doi:10.5489/cuaj.8588

C. GT02-Hereditary-Cancer-Susceptibility-10-30-2022.pdf. Accessed January 18, 2024. https://providers.carelonmedicalbenefitsmanagement.com/genetictesting/wp-content/uploads/sites/15/2022/09/GT02-Hereditary-Cancer-Susceptibility-10-30-2022.pdf

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GALAD score

Biomarker name: GALAD score [A].

Biomarker context: Hepatocellular carcinoma (HCC) screening and early detection often involve the use of serological biomarker testing, in many cases combined with ultrasound imaging. Alpha-fetoprotein (AFP) is the most used biomarker for this purpose, but its sensitivity is still low. Researchers have constructed models, combining additional factors, to improve this situation. The GALAD score integrates gender, age and three serum biomarkers [AFP, lens culinaris agglutinin-reactive subfraction of AFP (AFP-L3) and des-gamma-carboxy prothrombin (DCP)] to construct an early diagnostic model. Its efficacy for detecting HCC has been evaluated in many populations, leading to evaluate its overall diagnostic accuracy.

Test definition: The GALAD score is a serum biomarker-based model that includes five variables (gender, age, AFP-L3, AFP and DCP), used to predict the probability of having HCC in patients with chronic liver disease for early diagnosis.

Results of the search

After doing a search for 'GALAD score' in the TRIP database, we found seven publications, of which two were appropriate for the test definition.

Evidence of clinical utility for the test

Evidence 1: A review of 2022 Chinese clinical guidelines on the management of hepatocellular carcinoma: updates and insights [B].

This document was published in March 2023 by the Hepatobiliary Surgery and Nutrition journal. No TRIP score was assigned. The guideline is mostly focused on management of the tumours, but also states the recommended surveillance strategy in the country, which is ultrasonography combined with α-fetoprotein (AFP) every 6 months. Nevertheless, it also recommends using serum biomarker-based models such as GALAD score for HCC surveillance and early diagnosis, especially in high-risk populations, such as individuals with liver cirrhosis, hepatitis B or C infection, alcohol misuse, non-alcoholic steatohepatitis (NASH), or a family history of HCC.

Evidence 2: Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases [C].

This document was published in August 2018 by the American Association for the Study of Liver Disease. It received a TRIP score of 3.

The guideline explores the potential use of the GALAD model in phase II biomarker investigations, specifically in case-control designs. Nevertheless, it underscores the need for additional assessment via phase III and IV trials in extensive cohort settings to thoroughly evaluate its efficacy as a diagnostic tool for HCC surveillance.

Conclusion

In conclusion, the GALAD score shows promise as a blood-derived biomarker for the

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diagnosis of HCC, particularly in populations where the illness is very likely to manifest. Evidence exists to support its clinical utility.

Guideline Central search terms used: galad; galad score

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: ((“liver cancer” OR "hepatocellular carcinoma") AND ("galad") AND ("prevent" OR "screen" OR "early diagnos")), 2013

A. Guan MC, Zhang SY, Ding Q, et al. The Performance of GALAD Score for Diagnosing Hepatocellular Carcinoma in Patients with Chronic Liver Diseases: A Systematic Review and Meta-Analysis. *JCM*. 2023;12(3):949. doi:10.3390/jcm12030949

B. Xie DY, Zhu K, Ren ZG, Zhou J, Fan J, Gao Q. A review of 2022 Chinese clinical guidelines on the management of hepatocellular carcinoma: updates and insights. *Hepatobiliary Surg Nutr*. 2023;12(2):216-228. doi:10.21037/hbsn-22-469

C. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2018;68(2):723-750. doi:10.1002/hep.29913

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GREM1 gene

Biomarker name: *GREM1* gene [A].

Biomarker context: Colorectal cancer (CRC) is the most prevalent cancer of digestive system with multifactorial etiology and complex pathological indexes. Several studies have revealed that miRNAs are involved in crucial pathways and comprehensive biological processes, including apoptosis, reprogramming gene expression, tumourigenesis, diseases development, and cancer pathogenesis. MiRNAs are a class of non-coding RNAs involved in modulating biological processes through alteration in post-translational regulation. MiRNAs bind primarily to the 3' untranslated region (3' UTR) of the genes through seed sequences and regulating gene expression. The occurrence of single-nucleotide variation in miRNA binding sites could affect carcinogenesis risk, survival score, and cancer invasion.

Test definition: genetic test to identify variation in the *GREM1* gene in the general population for an increased risk of CRC.

Results of the search: No guidelines were identified using the search terms in Guideline Central. In TRIP, eight guidelines were found by the search terms. Of the eight guidelines, seven mentioned genetic testing using *GREM1* in contexts other than primary prevention or early detection of CRC. One guideline considered *GREM1* in hereditary cancer screening.

Evidence 1: Hereditary Cancer Testing Eligibility Criteria: Version 3 [B].

This document is published by the Hereditary Cancer Testing Eligibility Working Group within Ontario Health Cancer Care in 2022. It serves as a companion to Ontario's standardised Hereditary Cancer Testing Gene List for genetics professionals to determine hereditary cancer testing eligibility for early diagnosis. The *GREM1* gene is recommended to be included in germline panel testing for hereditary polyposis and for Lynch Syndrome. The guideline has a TRIP score of 5.

Conclusion: One document included *GREM1* as part of a multi-gene panel for hereditary cancer testing among those that may need it according to a previous clinical specific assessment. However, miRNA binding sites were not mentioned.

Search terms used for this biomarker

Guideline Central search terms used: GREM1 AND colorectal

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: colorectal cancer

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: GREM1

A. Hajibabaie F, Abedpoor N, Assareh N, Tabatabaiefar MA, Shariati L, Zarrabi A. The Importance of SNPs at miRNA Binding Sites as Biomarkers of Gastric and Colorectal Cancers: A Systematic Review. JPM. 2022;12(3):456. doi:10.3390/jpm12030456

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B. Holliday H. Ontario Health (Cancer Care Ontario), 2022. Hereditary Cancer Testing Eligibility Criteria: Version 3 https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/70161

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Homeobox 13 (*HOXB13*) gene

Biomarker name: Homeobox 13 (*HOXB13*) gene [A].

Biomarker context: Genetic testing in prostate cancer (PCa) is becoming standard of care among those men with familial history of PCa or personal history of other tumours. It can provide key information for clinical management, as well as offering crucial insights into familial cancer risk. Identification of germline gene alterations in PCa patients provides an opportunity for cascade testing in family members, opening up avenues for cancer prevention and early diagnosis among those who may also carry the same germline gene alterations.

Test definition: Genetic test to identify variants in the *HOXB13* gene to indicate an increased risk of PCa.

Results of the search: No results were identified using the search terms in Guideline Central. Eleven guidelines were identified in TRIP, of which three were relevant to the test definition.

Evidence 1: 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer [B].

This document, with a TRIP score of 6, considers genetic testing during various stages of PCa. It recommends that people at high-risk of PCa should undergo germline testing as soon as their risk level is determined. Those considered to be at high risk included people with a positive family history of prostate or related cancer (such as breast, ovarian, colorectal and endometrial), those with a personal history of associated cancers, those with Ashkenazi Jewish heritage and those with ductal, intraductal or cribriform pathology. The guideline recommends that *HOXB13* should be included in the germline gene panel test for PCa.

Evidence 2: Hereditary Cancer Testing Eligibility Criteria: Version 3 [C].

This document is published by the Hereditary Cancer Testing Eligibility Working Group within Ontario Health Cancer Care in 2022, has a TRIP score of 5. It serves as a companion to Ontario's standardised Hereditary Cancer Testing Gene List for genetics professionals to determine hereditary cancer testing eligibility for early diagnosis. The *HOXB13* gene is recommended to be included in germline panel testing. It has a TRIP score of 5.

Evidence 3: Carelon Medical Hereditary Cancer Testing 2023-02-12 to 11-04 [D].

This guideline considers multiple related cancers including Pca, has a TRIP score of 0. It recommends germline genetic testing of specific genes including HOXB13 to inform the assessment of hereditary risk of prostate cancer. The screening is considered medically necessary in individuals with any of the following:

- Metastatic prostate cancer
- Three or more first-degree relatives with prostate cancer
- High-risk localised prostate cancer and EITHER of the following:
    - Ashkenazi Jewish ancestry

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- Two or more first-degree relatives with breast, ovarian, or pancreatic cancer or Lynch syndrome spectrum cancer in any relatives on the same side of the family
- Personal history of prostate cancer diagnosed before age 60 AND at least one first-degree relative with prostate cancer diagnosed before age 60
- One or more first-degree relatives with prostate cancer diagnosed before age 60 or who died of prostate cancer
- Personal history of one or more pathogenic variants found by tumour somatic testing of any of the following genes: *BRCA2, BRCA1, CHEK2*, or *ATM*

Conclusion: Multiple guidelines were identified that considered the *HOXB13* gene in the context of risk identification and stratification in PCa. The use of the *HOXB13* gene in a hereditary PCa multi-gene panel is recommended.

Search terms used for this biomarker

Guideline Central search terms used: HOXB13 AND prostate

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: prostate cancer

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: HOXB13

A. Marino F, Totaro A, Gandi C, et al. Germline mutations in prostate cancer: a systematic review of the evidence for personalized medicine. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3

B. Rendon RA, Selvarajah S, Wyatt AW, et al. 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer. CUAJ. 2023;17(10):314-325. doi:10.5489/cuaj.8588

C. Holliday H. Ontario Health (Cancer Care Ontario) , 2022. Hereditary Cancer Testing Eligibility Criteria: Version 3

https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/70161

D. GT02-Hereditary-Cancer-Susceptibility-10-30-2022.pdf. Accessed January 18, 2024. https://providers.carelonmedicalbenefitsmanagement.com/genetictesting/wp-content/uploads/sites/15/2022/09/GT02-Hereditary-Cancer-Susceptibility-10-30-2022.pdf

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MLH1 gene

Biomarker name: *MLH1* gene [A].

Biomarker context: Genetic testing in prostate cancer (PCa) is becoming standard of care among those men with familial history of PCa or personal history of other tumours. It can provide key information for clinical management, as well as offering crucial insights into familial cancer risk. Identification of germline gene alterations in PCa patients provides an opportunity for cascade testing in family members, opening up avenues for cancer prevention and early diagnosis among those who may also carry the same germline gene alterations.

Test definition: A genetic test to identify a variant in the *MLH1* gene indicating an increased risk of PCa.

Results of the search: Two guidelines were identified in Guideline Central however neither were relevant to the test definition. Forty-five results were identified using the search terms in TRIP and three documents were relevant to the test definition.

Evidence 1: 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer [B].

This document considers genetic testing during various stages of PCa and has a TRIP score of six. It recommends that people at high-risk of PCa should undergo germline testing as soon as their risk level is determined. Those considered to be at high risk included people with a positive family history of prostate or related cancer (such as breast, ovarian, colorectal, and endometrial), those with a personal history of associated cancers, those with Ashkenazi Jewish heritage and those with ductal, intraductal or cribriform pathology. The guideline recommends that *MLH1* should be included in the germline gene panel test for PCa.

Evidence 2: Hereditary Cancer Testing Eligibility Criteria: Version 3 [C].

This document is published by the Hereditary Cancer Testing Eligibility Working Group within Ontario Health Cancer Care in 2022. It serves as a companion to Ontario's standardised Hereditary Cancer Testing Gene List for genetics professionals to determine hereditary cancer testing eligibility for early diagnosis. The *MLH1* gene is recommended to be included in germline panel testing. It has a TRIP score of five.

Evidence 3: Carelon Medical Hereditary Cancer Testing 2023-02-12 to 11-04 [D].

This guideline considers multiple related cancers including PCa. It recommends germline genetic testing of specific genes including *MLH1* to inform the assessment of hereditary risk of prostate cancer. The screening is considered medically necessary in individuals with any of the following:

- Metastatic prostate cancer
- Three or more first-degree relatives with prostate cancer
- High-risk localised prostate cancer and EITHER of the following:
    - Ashkenazi Jewish ancestry

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- Two or more first-degree relatives with breast, ovarian, or pancreatic cancer or Lynch syndrome spectrum cancer in any relatives on the same side of the family
- Personal history of prostate cancer diagnosed before age 60 AND at least one first-degree relative with prostate cancer diagnosed before age 60
- One or more first-degree relatives with prostate cancer diagnosed before age 60 or who died of prostate cancer
- Personal history of one or more pathogenic variants found by tumour somatic testing of any of the following genes: *BRCA2, BRCA1, CHEK2,* or *ATM*

Conclusion: Multiple guidelines were identified that considered the *MLH1* gene in the context of risk identification and stratification in PCa. The use of the *MLH1* gene in a multi-gene panel is recommended.

Search terms used for this biomarker

Guideline Central search terms used: MLH1 AND prostate

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: prostate cancer

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: MLH1

A. Marino F, Totaro A, Gandi C, et al. Germline mutations in prostate cancer: a systematic review of the evidence for personalized medicine. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3

B. Rendon RA, Selvarajah S, Wyatt AW, et al. 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer. CUAJ. 2023;17(10):314-325. doi:10.5489/cuaj.8588

C. Holliday H. Ontario Health (Cancer Care Ontario) , 2022. Hereditary Cancer Testing Eligibility Criteria: Version 3. https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/70161

D. PDF-Hereditary-Cancer-Testing-2023-11-05.pdf. Accessed January 18, 2024. https://guidelines.carelonmedicalbenefitsmanagement.com/wp-content/uploads/2023/07/PDF-Hereditary-Cancer-Testing-2023-11-05.pdf

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MSH2 gene

Biomarker name: *MSH2* gene [A].

Biomarker context: Genetic testing in prostate cancer (PCa) is becoming standard of care among those men with familial history of PCa or personal history of other tumours. It can provide key information for clinical management, as well as offering crucial insights into familial cancer risk. Identification of germline gene alterations in PCa patients provides an opportunity for cascade testing in family members, opening up avenues for cancer prevention and early diagnosis among those who may also carry the same germline gene alterations.

Test definition: A genetic test to identify variation in the *MSH2* gene to indicate an increased risk of PCa.

Results of the search: Two guidelines were identified in Guideline Central however neither matched the test definition. Forty-six guidelines were identified using the search terms in TRIP, of which two were relevant to the test definition.

Evidence 1: 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer [B].

This document considers genetic testing during various stages of PCa and has a TRIP score of six. It recommends that people at high-risk of PCa should undergo germline testing as soon as their risk level is determined. Those considered to be at high risk included people with a positive family history of prostate or related cancer (such as breast, ovarian, colorectal, and endometrial), those with a personal history of associated cancers, those with Ashkenazi Jewish heritage and those with ductal, intraductal or cribriform pathology. The guideline recommends that *MSH2* should be included in the germline gene panel test for PCa.

Evidence 2: Hereditary Cancer Testing Eligibility Criteria: Version 3 [C].

This document is published by the Hereditary Cancer Testing Eligibility Working Group within Ontario Health Cancer Care in 2022. It serves as a companion to Ontario's standardised Hereditary Cancer Testing Gene List for genetics professionals to determine hereditary cancer testing eligibility for early diagnosis. The *MSH2* gene is recommended to be included in germline panel testing. It has a TRIP score of 5.

Conclusion: *MSH2* is recommended for use in screening for PCa as part of established hereditary PCa multi-gene screening panels. Evidence considering its clinical use outside of this was not identified.

Search terms used for this biomarker

Guideline Central search terms used: MSH2 AND prostate

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: prostate cancer

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: MSH2

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A. Marino F, Totaro A, Gandi C, et al. Germline mutations in prostate cancer: a systematic review of the evidence for personalized medicine. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3

B. Rendon RA, Selvarajah S, Wyatt AW, et al. 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer. CUAJ. 2023;17(10):314-325. doi:10.5489/cuaj.8588

C. Holliday H. Ontario Health (Cancer Care Ontario), 2022. Hereditary Cancer Testing Eligibility Criteria: Version 3

https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/70161

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MSH6 gene

Biomarker name: *MSH6* gene [A].

Biomarker context: Genetic testing in prostate cancer (PCa) is becoming standard of care among those men with familial history of PCa or personal history of other tumours. It can provide key information for clinical management, as well as offering crucial insights into familial cancer risk. Identification of germline gene alterations in PCa patients provides an opportunity for cascade testing in family members, opening up avenues for cancer prevention and early diagnosis among those who may also carry the same germline gene alterations.

Test definition: A genetic test to identify a variant in the *MSH6* gene to indicate an increased risk of PCa.

Results of the search: Two guidelines were identified in Guideline Central however neither matched the test definition. Forty-six guidelines were identified using the search terms in TRIP, of which two were relevant to the test definition.

Evidence 1: 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer [B].

This document considers genetic testing during various stages of PCa. It has a TRIP score of six. It recommends that people at high-risk of PCa should undergo germline testing as soon as their risk level is determined. Those considered to be at high risk included people with a positive family history of prostate or related cancer (such as breast, ovarian, colorectal, and endometrial), those with a personal history of associated cancers, those with Ashkenazi Jewish heritage and those with ductal, intraductal or cribriform pathology. The guideline recommends that *MSH6* should be included in the germline gene panel test for PCa.

Evidence 2: Hereditary Cancer Testing Eligibility Criteria: Version 3 [C].

This document is published by the Hereditary Cancer Testing Eligibility Working Group within Ontario Health Cancer Care in 2022. It serves as a companion to Ontario's standardised Hereditary Cancer Testing Gene List for genetics professionals to determine hereditary cancer testing eligibility for early diagnosis. The *MSH6* gene is recommended to be included in germline panel testing. The guideline has a TRIP score of 5.

Conclusion: *MSH6* is recommended for use in screening for PCa as part of established hereditary PCa multi-gene screening panels. Evidence considering its clinical use outside of this was not identified.

Search terms used for this biomarker

Guideline Central search terms used: MSH6 AND prostate

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: prostate cancer

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: MSH6

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A. Marino F, Totaro A, Gandi C, et al. Germline mutations in prostate cancer: a systematic review of the evidence for personalized medicine. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3

B. Rendon RA, Selvarajah S, Wyatt AW, et al. 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer. CUAJ. 2023;17(10):314-325. doi:10.5489/cuaj.8588

C. Holliday H. Ontario Health (Cancer Care Ontario), 2022. Hereditary Cancer Testing Eligibility Criteria: Version 3. https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/70161

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PALB2 gene

Biomarker name: *PALB2* gene [A].

Biomarker context: Genetic testing in prostate cancer (PCa) is becoming standard of care among those men with familial history of PCa or personal history of other tumours. It can provide key information for clinical management, as well as offering crucial insights into familial cancer risk. Identification of germline gene alterations in PCa patients provides an opportunity for cascade testing in family members, opening up avenues for cancer prevention and early diagnosis among those who may also carry the same germline gene alterations.

Test definition: Genetic test to identify variants in the *PALB2* gene indicating an increased risk of PCa

Results of the search: The search terms identified three guidelines in Guideline Central however none were relevant to the test definition and focussed on either the wrong cancer type or disease management rather than prevention. Thirty-four results were found using the search terms in TRIP. Two were relevant to the test definition. The remaining guidelines considered either the wrong disease, disease management or oncological imaging.

Evidence 1: 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer [B].

This document considers genetic testing during various stages of PCa. The guideline has a TRIP score of six. It recommends that people at high-risk of PCa should undergo germline testing as soon as their risk level is determined. Those considered to be at high risk included people with a positive family history of prostate or related cancer (such as breast, ovarian, colorectal, and endometrial), those with a personal history of associated cancers, those with Ashkenazi Jewish heritage and those with ductal, intraductal or cribriform pathology. The guideline recommends that *PALB2* should be included in the germline gene panel test for PCa.

Evidence 2: Clinical Appropriateness Guidelines Genetic Testing for Hereditary Cancer Susceptibility [C].

This document was published in 2023 by the American organisation Carelon Health and has a TRIP score of zero. It discusses indications for hereditary testing in specific cancers. *PALB2* should always be included in multi-gene panels to be used in patients that fit the eligibility criteria. Patients at high risk of hereditary breast and ovarian cancer syndromes, which in this definition included prostate cancer, should undergo genetic testing to determine their risk of developing the disease.

Conclusion: The use of *PALB2* in testing to identify people at increased risk of PCa is recommended by the guidelines identified however it is only considered within hereditary PCa multi-gene screening panels not in isolation.

Search terms used for this biomarker

Guideline Central search terms used: PALB2 prostate

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TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: prostate cancer

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: PALB2

A. Marino F, Totaro A, Gandi C, et al. Germline mutations in prostate cancer: a systematic review of the evidence for personalized medicine. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3

B. Rendon RA, Selvarajah S, Wyatt AW, et al. 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer. CUAJ. 2023;17(10):314-325. doi:10.5489/cuaj.8588

C. GT02-Hereditary-Cancer-Susceptibility-10-30-2022.pdf. Accessed January 18, 2024. https://providers.carelonmedicalbenefitsmanagement.com/genetictesting/wp-content/uploads/sites/15/2022/09/GT02-Hereditary-Cancer-Susceptibility-10-30-2022.pdf

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PMS2 gene

Biomarker name: *PMS2* gene [A].

Biomarker context: Genetic testing in prostate cancer (PCa) is becoming standard of care among those men with familial history of PCa or personal history of other tumours. It can provide key information for clinical management, as well as offering crucial insights into familial cancer risk. Identification of germline gene alterations in PCa patients provides an opportunity for cascade testing in family members, opening up avenues for cancer prevention and early diagnosis among those who may also carry the same germline gene alterations.

Test definition: A genetic test to identify variants in the *PMS2* gene to identify an increased risk of PCa.

Results of the search: Two guidelines were identified in Guideline Central however neither met the test definition. Thirty-eight results were found in TRIP, of which two were relevant to the test definition.

Evidence 1: 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer [B].

This document considers genetic testing during various stages of PCa. It recommends that people at high-risk of PCa should undergo germline testing as soon as their risk level is determined. Those considered to be at high risk included people with a positive family history of prostate or related cancer (such as breast, ovarian, colorectal, and endometrial), those with a personal history of associated cancers, those with Ashkenazi Jewish heritage and those with ductal, intraductal or cribriform pathology. The guideline recommends that *PMS2* should be included in the germline gene panel test for PCa. This guideline has a TRIP score of 6.

Evidence 2: Hereditary Cancer Testing Eligibility Criteria: Version 3 [C].

This document is published by the Hereditary Cancer Testing Eligibility Working Group within Ontario Health Cancer Care in 2022. It serves as a companion to Ontario's standardised Hereditary Cancer Testing Gene List for genetics professionals to determine hereditary cancer testing eligibility for early diagnosis. The *PMS2* gene is recommended to be included in germline panel testing. The evidence has a TRIP score of 5.

Conclusion: Two guidelines were identified that considered the *PMS2* gene in the context of risk identification and stratification in PCa. The use of the *PMS2* gene in a hereditary PCa multi-gene panel is recommended if germline mutations are suspected.

Search terms used for this biomarker

Guideline Central search terms used: PMS2 AND prostate

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: prostate cancer

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

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TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: PMS2

A. Marino F, Totaro A, Gandi C, et al. Germline mutations in prostate cancer: a systematic review of the evidence for personalized medicine. Prostate Cancer Prostatic Dis. 2023;26(4):655-664. doi:10.1038/s41391-022-00609-3

B. Rendon RA, Selvarajah S, Wyatt AW, et al. 2023 Canadian Urological Association guideline: Genetic testing in prostate cancer. CUAJ. 2023;17(10):314-325. doi:10.5489/cuaj.8588

C. Holliday H. Ontario Health (Cancer Care Ontario), 2022. Hereditary Cancer Testing Eligibility Criteria: Version 3 https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/70161

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MLH3 gene

Biomarker name: variation in the *MLH3* gene [A].

Biomarker context*:* Colorectal cancer (CRC) is the most prevalent cancer of digestive system with multifactorial etiology and complex pathological indexes. Several studies have revealed that miRNAs are involved in crucial pathways and comprehensive biological processes, including apoptosis, reprogramming gene expression, tumourigenesis, diseases development, and cancer pathogenesis. MiRNAs are a class of non-coding RNAs involved in modulating biological processes through alteration in post-translational regulation. MiRNAs bind primarily to the 3' untranslated region (3' UTR) of the genes through seed sequences and regulating gene expression. The occurrence of single-nucleotide variation (SNP) in miRNA binding sites could affect carcinogenesis risk, survival score, and cancer invasion.

Test definition: genetic test to identify variation of the *MLH3* gene, especially in the miRNA binding sites, in the general population indicating an increased risk of CRC.

Results of the search: The search terms returned no guideline results in Guideline Central. One guideline was identified in TRIP that recommends the use of the gene in hereditary cancer testing as part of a multi-gene panel.

Evidence 1: Hereditary Cancer Testing Eligibility Criteria: Version 3 [B].

This document is published by the Hereditary Cancer Testing Eligibility Working Group within Ontario Health Cancer Care in 2022. It serves as a companion to Ontario's standardised Hereditary Cancer Testing Gene List for genetics professionals to determine hereditary cancer testing eligibility for early diagnosis. The *MLH3* gene is recommended to be included in germline panel testing for hereditary polyposis and for Lynch Syndrome. The guideline has a TRIP score of 5.

Conclusion: One document included *MLH3* as part of a multi-gene panel for hereditary cancer testing among those that may need it according to a previous clinical specific assessment. However, miRNA binding sites were not mentioned.

Search terms used for this biomarker

Guideline Central search terms used: MLH3 AND colorectal

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: colorectal cancer

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: MLH3

A. Hajibabaie F, Abedpoor N, Assareh N, Tabatabaiefar MA, Shariati L, Zarrabi A. The Importance of SNPs at miRNA Binding Sites as Biomarkers of Gastric and Colorectal Cancers: A Systematic Review. JPM. 2022;12(3):456. doi:10.3390/jpm12030456

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B. Holliday H. Ontario Health (Cancer Care Ontario), 2022. Hereditary Cancer Testing Eligibility Criteria: Version 3 https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/70161

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Tyrer-Cuzick model

Biomarker name: Tyrer-Cuzick model or IBIS model [A].

Biomarker context: Stratification using a breast cancer risk prediction model has the potential to identify women at increased risk of breast cancer, which would allow for screening tailored to those most likely to benefit. Among these, the Tyrer-Cuzick Model measures the likelihood that a woman will have risk cancer due to harbouring specific gene mutations related to breast cancer, helping to personalise the indication of genetic testing. This is done through an advanced algorithm that incorporates women's personal medical and reproductive history (age, weight, height, history of hormone use, age of first menstruation, age of birth of first child if applicable, age of menopause if applicable and age of cancer diagnosis if applicable), familial and personal cancer history alongside breast density and biopsy results.

Test definition: The Tyrer-Cuzick model is a statistical tool that estimates an individual risk of developing breast cancer in the general adult female population.

Results of the search:

The search terms returned ninety-one guidelines in Guideline Central using the broader term of "breast cancer", of which two were relevant to our test definition. The guidelines that were not selected did not match the test definition in terms of the biomarker, the disease of interest and the prevention level. The search strategy yielded sixteen guidelines in TRIP and only one matched the test definition.

Evidence of clinical utility for the test

Evidence 1: Hereditary Breast and Ovarian Cancer Syndrome [B].

The document was published in September 2017 by the American College of Obstetricians and Gynecologists in collaboration with the Society of Gynecologic Oncology. The original country of publication is the United States of America.

This guideline focuses on breast cancer genetic testing and presents recommendations to help genetic counselling in women with increased risk of breast cancer. In relation to our biomarker, the guideline states that several risk assessment models, such as the Tyrer-Cuzick model, should be used to determine eligibility for genetic testing and identification of candidates in the family to proceed with genetic testing.

Evidence 2: Breast Cancer Risk Assessment and Screening in Average-Risk Women [C].

This document was published in July 2017 by the American College of Obstetricians and Gynecologists. The original country of publication is the United States of America.

The guideline discusses breast cancer risk assessment, reviews breast cancer screening guidelines in average-risk women, outlines controversies surrounding breast cancer screening and presents recommendations to assist women in making decisions surrounding breast cancer screening. In connection with the Tyrer-Cuzick model, the guideline claims that this risk assessment model should be used to determine the risk of developing breast cancer and assess the eligibility of genetic testing.

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Evidence 3: Overview of the Implications and Implementation of NICE guidelines on familial breast cancer [D].

The Association of Breast Surgery published this document in November 2015. The original country of publication was the United Kingdom (UK). The document was given a TRIP score of 0.

This guideline reviews the NICE recommendations on risk assessment, thresholds for genetic testing, screening, surveillance, risk reduction and treatment strategies for women with a familial history of breast cancer or women diagnosed with breast cancer. Among the recommendations, it states that risk assessment models, such as the Tyrer-Cuzick model, can be used to determine the risk of developing breast cancer and assess the eligibility for genetic testing.

Conclusion:
The guidelines are supportive of the use of the Tyrer-Cuzick model and other risk assessment models to estimate the risk of developing breast cancer. In this case, this model is mostly recommended as a tool to help clinicians to assess the eligibility for genetic testing or to advise appropriate individual surveillance pathways.

Guideline Central search terms used: "breast cancer"

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: ("breast cancer" AND "tyrer-cuzick" AND ("prevent" OR "screen" OR "early diagnos")) from_date:2013

A. Vilmun BM, Vejborg I, Lynge E, et al. Impact of adding breast density to breast cancer risk models: A systematic review. *Eur J Radiol*. 2020;127:109019. doi:10.1016/j.ejrad.2020.109019

B. American College of Obstetricians and Gynecologists, Society of Gynecologic Oncology. Hereditary Breast and Ovarian Cancer Syndrome. *Obstet Gynecol*. 2017;130(3):110-126. doi:10.1097/00006250-200309000-00057

C. American College of Obstetricians and Gynecologists. Breast Cancer Risk Assessment and Screening in Average-Risk Women. *Obstet Gynecol*. 2017;130(1):1-16. doi:10.1097/00006250-200307000-00051

D. Turton P, Grimsey E, Sekharan C. *Overview of the Implications and Implementation of Nice Guidelines on Familial Breast Cancer*. Association of Breast surgery; 2015.

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Stockholm3 test

Biomarker name: Stockholm3 test [A].

Biomarker context: There are several emerging blood-based tests to estimate prostate cancer risk developed for use with traditional prostate biopsies. These tests have shown the potential to improve the diagnostic accuracy compared with using Prostate-Specific Antigen (PSA) alone for biopsy referral. Among these emerging tests is the Stockholm3 test, which incorporates clinical variables (age and previous prostate biopsy), plasma protein concentrations (PSA, free PSA, human kallikrein 2, β-microseminoprotein, and growth-differentiation factor-15), and a polygenic risk score derived from single-nucleotide polymorphisms to yield a percentage risk of clinically significant prostate cancer.

Test definition: Stockholm3 is a blood-based diagnostic test to predict risk of prostate cancer in men aged 45 to 74 years with PSA of at least 1.5 ng/ml and no previous prostate cancer diagnosis.

Results of the search:

The search terms returned forty-one guidelines in Guideline Central using the broader term of “prostate cancer”, of which one was relevant to our test definition. The guidelines that were not selected did not match the test definition in terms of the biomarker, the disease of interest and the prevention level. The search strategy yielded one useful guideline in TRIP.

Evidence of clinical utility for the test

Evidence 1: Early detection of prostate cancer [B].

The document was published in April 2023 by the American Urological Association in collaboration with the Society of Urologic Oncology. The original country of publication is the United States of America.

This guideline covers recommendations on the early detection of prostate cancer and provides a framework to facilitate clinical decision-making in the implementation of prostate cancer screening, biopsy and follow-up. In relation to our biomarker, the guideline states that clinicians should use a PSA-based test as the first test for prostate cancer screening, including the Stockholm-3 test, which has more specificity than PSA alone. However, it also highlights that while this novel test seems promising, further validation in diverse populations is necessary to move forward into practice.

Evidence 2: EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer [C].

This document was published in March 2023 by the European Association of Urology and is an update of the previous version published in 2022. It is endorsed by different European Urological, Radiography and Oncology organisations such as the European association of Nuclear Medicine, the European Society of Urogenital Radiology, and the European Society for Radiotherapy and Oncology. The document was originally presented in the EAU annual congress in Milan. It has TRIP score of 8.

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This guideline document aims to assist medical professionals in the evidence-based management of prostate cancer in terms of screening, diagnosis and local treatment. In relation to the Stockholm3 test, the guideline states that in asymptomatic men with a PSA level between 3-10 ng/ mL and a normal Digital Rectal Exam (DRE), a risk calculator, including the Stockholm3 test, may be used for biopsy indication, if this is correctly calibrated to the population prevalence.

Conclusion:

The guidelines are supportive of the use of the Stockholm3 test but whilst one recommends its use as a first line screening method, the other recommends using PSA alone as the first line screening technique. However, if the PSA levels are between 3-10 ng/mL and the patient has a normal DRE, the Stockholm3 test could be used for biopsy indication. There is also a consensus that the Stockholm3 test should be further validated in diverse populations in order to move forward into clinical practice.

Guideline Central search terms used: Prostate cancer

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome:
("prostate cancer" AND "stockholm3" AND ("prevent" OR "screen" OR "early diagnos")) from_date:2013

A. Nordström T, Discacciati A, Bergman M, et al. Prostate cancer screening using a combination of risk-prediction, MRI, and targeted prostate biopsies (STHLM3-MRI): a prospective, population-based, randomised, open-label, non-inferiority trial. *Lancet Oncol*. 2021;22(9):1240-1249. doi:10.1016/S1470-2045(21)00348-X

B. Wei JT, Barocas D, Carlsson S, et al. Early Detection of Prostate Cancer: AUA/SUO Guideline. *J Urol*. 2023;210(1):46-53. doi:10.1097/JU.0000000000003491

C. Mottet N, P. Cornford, R.C.N. van den Bergh, et al. EAU - EANM - ESTRO ESUR - ISUP - SIOG Guidelines on Prostate Cancer. *Eur Assoc Urol*. Published online April 2023. https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2023_2023-03-27-131655_pdvy.pdf

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3.1.3 Tests with evidence – clinical utility not supported, cancer

ExoDx Prostate IntelliScore test (EPI test)

Biomarker name: ExoDx Prostate IntelliScore test (EPI test) [A, B]

Biomarker context: Prostate cancer screening with PSA has many limitations, and its clinical utility is still under debate. Researchers are looking for alternative biomarkers that may help to identify clinically relevant prostate cancer cases from those that will not become aggressive tumours. One of the strategies has used exosomes secreted by cancer cells, as they may may contain mRNA diagnostic for high-grade PCa. The ExoDx Prostate (IntelliScore) (EPI) test is a non-invasive liquid biopsy that quantifies three RNA targets in urine exosomes. This test is a non-invasive risk assessment tool for detection of high-grade prostate cancer (HGPC) that does not require pre-collection digital rectal, and which is intended to inform whether to proceed with prostate biopsy in men aged 50 years or more with a PSA level between 2-10 ng/mL.

Test definition: ExoDx Prostate IntelliScore (EPI test) for improved screening of prostate cancer in men 50 years or older with a PSA between 2-10 ng/ml.

Results of the search

No evidence was available in the form of guidelines or health technology assessments (HTA). One cost effectiveness evaluation (CEA) was found for this test definition.

The search terms used for this biomarker´s clinical utility produced zero results in Guideline Central. Twenty-two guidelines were found in TRIP, twenty did not focus on the disease of interest and one did not match the test definition.

In terms of HTA and CEA documents, thirty-six results were retrieved from TRIP**,** but none focused on the disease of interest, prevention level or type of document (HTA or CEA). We were not able to generate any valid results from CRD or the International HTA database using the defined search terms. One result was retrieved from CEA that matched the test definition.

Evidence of clinical utility for the test:

Evidence 1: EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer [C].

This document was published in March 2023 by the European Association of Urology and is an update of the previous version published in 2022. It is endorsed by different European Urological, Radiography and Oncology organisations such as the European association of Nuclear Medicine, European Society of Urogenital Radiology or the European Society for Radiotherapy and Oncology. It has a TRIP score of 8.

This guideline document aims to assist medical professionals in the evidence-based management of prostate cancer in terms of screening, diagnosis and local treatment. It

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states that Exodx test is currently considered investigational and may not be widely adopted as part of routine clinical practice.

Evidence 2: Incorporating Biomarkers into the Primary Prostate Biopsy Setting: A Cost-Effectiveness Analysis [D].

This document was published in August 2018 by the American Urological Association Education and Research at the Journal of Urology. The original country of publication is the United States of America.

This CEA document compares the cost-effectiveness of using the Prostate Health Index (PHI), 4Kscore, SelectMDx or the EPI test as supplementary tests in men with elevated PSA to determine the need for biopsy. In relation to our biomarker, it states that the use of the EPI test to determine the need for biopsy in men with elevated PSA is a potentially cost-effective strategy.

Conclusion:

Even though some reports indicate that the use of ExoDx Prostate IntelliScore (EPI) test could be a cost-effective strategy, very recent guidelines currently consider this test as investigational and indicate that it still may not be widely adopted as part of routine clinical practice. Also, the use of MRI is likely to affect the clinical utility of above-mentioned biomarkers.

Guideline Central search terms used: EPI ; ExoDx Prostate IntelliScore

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome:
("prostate cancer" AND ("epi" or "exodx prostate intelliscore") AND ("prevent" OR "screen" OR "early diagnos")) from_date:2013

HTA search terms for TRIP Advanced "ALL of these words" OR TRIP PICO Outcome:
("prostate cancer" AND ("exodx prostate intelliscore" or "epi") AND ("prevent" OR "screen" OR "early diagnos" "health technology assessment" "cost effective" "economic evaluat)) from_date:2013

Search terms used in CRD database: EPI; Exodx Prostate IntelliScore

HTA search terms used in International HTA database: EPI test; Exode prostate intelliscore

CEA search terms used in CEA registry: EPI test; Exodx prostate intelliscore

A. Tutrone R, Donovan MJ, Torkler P, et al. Clinical utility of the exosome based ExoDx Prostate(IntelliScore) EPI test in men presenting for initial Biopsy with a PSA 2-10 ng/mL. *Prostate Cancer Prostatic Dis*. 2020;23(4):607-614. doi:10.1038/s41391-020-0237-z

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B. Margolis E, Brown G, Partin A, et al. Predicting high-grade prostate cancer at initial biopsy: clinical performance of the ExoDx (EPI) Prostate Intelliscore test in three independent prospective studies. *Prostate Cancer Prostatic Dis*. 2022;25(2):296-301. doi:10.1038/s41391-021-00456-8

C. Mottet N, P. Cornford, R.C.N. van den Bergh, et al. EAU - EANM - ESTRO ESUR - ISUP - SIOG Guidelines on Prostate Cancer. *Eur Assoc Urol*. Published online April 2023. https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2023_2023-03-27-131655_pdvy.pdf

D. Sathianathen NJ, Kuntz KM, Alarid-Escudero F, et al. Incorporating Biomarkers into the Primary Prostate Biopsy Setting: A Cost-Effectiveness Analysis. *J Urol*. 2018;200(6):1215-1220. doi:10.1016/j.juro.2018.06.016

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LCDRAT prediction model

Biomarker name: Lung Cancer Death Risk Assessment Tool (LCDRAT) prediction model [A].

Biomarker context: Lung cancer screening using low dose computed tomography has been proposed as a tool to decrease lung cancer-specific mortality. The LCDRAT prediction model, based on data from the PLCO control group, is used for risk prediction intended to select individuals for screening based on the risk of lung cancer death. The model incorporates age, education, sex, race, smoking intensity, duration, and quit-years, BMI, family history of lung cancer, and self-reported emphysema to predict annual lung cancer risk. BMI is the only biomarker included in this prediction model.

Test definition: LCDRAT prediction model to identify patients at high risk of lung cancer death in adults for LDCT screening.

Results of the search

No results were identified in Guideline Central. The search terms yielded two results in the TRIP search, and only one matched the test definition.

Evidence of clinical utility of the test

Evidence 1: Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement [B].

This guideline, which has a TRIP score of 7 and were last revised in 2013, focus on the accuracy of LDCT for lung cancer screening, as well as the related benefits and hazards. They provide information on the ideal age range for screening beginning and ending, as well as suggested screening intervals. The guidelines also compare the relative advantages and disadvantages of different screening procedures to modified multivariate prediction models. According to the document, the USPSTF commissioned comparative modelling studies to explore screening benefits and hazards using risk prediction models in relation to age and smoking history. The LCDRAT was one of the models evaluated. It states that, while risk prediction algorithms expanded screening to older people, lowering lung cancer deaths, they also led to overdiagnosis at older ages, resulting in less years gained. Implementing advanced risk prediction models may hamper mass screening acceptance, and their performance is questionable when compared to age and smoking status. They reach the conclusion that utilizing complicated risk prediction models for eligibility may present implementation challenges, and there is inadequate data to indicate their superiority over age and smoking history criteria in improving outcomes.

Conclusion: There is not a specific recommendation of the clinical utility of this model. Based on the guideline, careful consideration and further evidence is needed to determine the clinical utility and effectiveness of complex prediction models in improving screening outcomes for lung cancer.

Guideline Central search terms used: LCDRAT

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: (("lung cancer") AND ("lcdrat" AND "risk prediction" AND "model") AND ("prevent" OR "screen" OR "early diagnos")) from_date:2013

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A. Toumazis I, Bastani M, Han SS, Plevritis SK. Risk-Based lung cancer screening: A systematic review. Lung Cancer. 2020;147:154-186. doi:10.1016/j.lungcan.2020.07.007

B. US Preventive Services Task Force, Krist AH, Davidson KW, et al. Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2021;325(10):962. doi:10.1001/jama.2021.1117

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The Michigan Prostate Score (MiPS)

Biomarker name: The Michigan Prostate Score (MiPS) or MyProstateScore (MPS) test [A].

Biomarker context: Various molecular biomarker tests have been developed in recent years as diagnostic techniques for the early and non-invasive identification of prostate cancer (PCa). Because urine is easier to collect and prostate cells are discharged directly into the urethra following digital rectal examination (DRE), the non-invasive detection of urine-related biomarkers has become a better alternative screening technique and a research focus. Some innovative urine indicators, such as Progensa Prostate Cancer Antigen 3 (PCA3), SelectMDX, ExoDx Prostate Intelliscore (EPI), Mi-ProstateScore (MiPS), and others, are being gradually employed for prostate cancer monitoring and detection. The Michigan Prostate Score (MiPS) is a test that combines serum PSA levels with urinary PCA3 and T2:ERG expression, which have been associated with prostate cancer. The MiPS assay tests for the presence of two prostate cancer biomarkers: PCA3 and TMPRSS2: ERG (T2: ERG) RNA in the urine after digital rectal examination.

Test definition: The MiPS is used to estimate an individual's risk of developing prostate cancer.

Results of the search

Upon conducting a search in TRIP, 24 guidelines were discovered. Among these, only one guideline was suitable for our test definition. The guidelines that were not selected, even though some discussed prostate cancer, did not mention the biomarker.

Evidence of clinical utility for the test

Evidence 1: EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer [B].

This document was published in March 2023 by the European Association of Urology and is an update of the previous version published in 2022. It is endorsed by different European Urological, Radiography and Oncology organisations such as the European association of Nuclear Medicine, European Society of Urogenital Radiology or the European Society for Radiotherapy and Oncology. It has a TRIP score of 8.

This guideline document aims to assist medical professionals in the evidence-based management of prostate cancer in terms of screening, diagnosis and local treatment. It states that the detection of TMPRSS2-ERG in urine, when combined with PCA3 expression and serum PSA, as in the MiPS, has shown improved cancer prediction. It notes that MiPS test is currently considered investigational and may not be widely adopted as part of routine clinical practice.

Conclusion

Although there are encouraging advancements in the utilisation of TMPRSS2-ERG fusion detection, as well as other indicators such as PCA3, for the early diagnosis of prostate cancer, specific tests like MiPS are still undergoing investigation. We did not find any recommendation that supports its clinical utility. Also, the use of MRI is likely to affect the clinical utility of above-mentioned biomarkers.

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Guideline Central search terms used: michigan prostate score; mips; prostate score

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: ((“prostate cancer”) AND (“mi-prostate scores” OR "mips") AND ("prevent" OR "screen" OR "early diagnos")) from_date:2013

A. Wang L, He W, Shi G, et al. Accuracy of novel urinary biomarker tests in the diagnosis of prostate cancer: A systematic review and network meta-analysis. *Front Oncol*. 2022;12:1048876. doi:10.3389/fonc.2022.1048876

B. Mottet N, P. Cornford, R.C.N. van den Bergh, et al. EAU - EANM - ESTRO ESUR - ISUP - SIOG Guidelines on Prostate Cancer. *Eur Assoc Urol*. Published online April 2023. https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2023_2023-03-27-131655_pdvy.pdf

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PanCan prediction model

Biomarker name: Pan-Canadian Early Detection of Lung Cancer Study (PanCan) prediction model [A].

Biomarker context: Lung cancer screening using low dose computed tomography (LDCT) has been proposed as a tool to decrease lung cancer-specific mortality. Risk-based lung cancer screening tries to select individuals based on their personal lung cancer risk to improve the sensitivity and specificity of LDCT screening. Numerous risk prediction models have been created to measure people's likelihood of developing lung cancer. The PanCan model is based on a cohort of patients in the Pan-Canadian Early Detection of Lung Cancer Study (PanCan), that tries to classify risk of cancer among those with lung nodules. Model predictors included age, sex, family history of lung cancer, emphysema, larger nodule size, location of the nodule in the upper lobe, part-solid nodule type, lower nodule count, and spiculation.

Test definition: PanCan prediction model to estimate the probability of lung cancer for screen-detected solidary pulmonary nodules in adult patients.

Results of the search

No results were identified in Guideline Central. The search terms yielded one result in the TRIP search that matched with the test definition.

Evidence of clinical utility of the test

Evidence 1: Management of screen-detected lung nodules: A Canadian partnership against cancer guidance document [B].

The document, with no TRIP score assigned, aims to provide healthcare practitioners with a comprehensive approach to managing lung nodules discovered with low-dose computed tomography (LDCT) in both opportunistic and programmatic lung cancer screening. The framework described is evidence-based and seeks to assist healthcare practitioners in properly dealing with these findings. It also gives background information for primary care physicians, allowing them to better explain results and future steps to patients. Finally, the guidelines identify issues that require consideration for future developments. The document identifies the PanCan model as a personalised approach for nodule management, describing its advantages and benefits. It gives a general statement on the personalised approach to manage screen-detected lung nodules, such as the PanCan: the approach has the potential to reduce resource utilization while also minimizing screening risk. Also, it has the possibility to save many people from unnecessary clinical examinations, lowering false positive rates and related harms while increasing efficiency. However, it remarks the importance of performing cost-effectiveness analyses to assess the benefits of personalised management models.

Conclusion

Currently there is no guidance regarding the biomarker's clinical utility. Based on the guidelines, careful consideration and additional data are required to determine the clinical value and efficacy of sophisticated prediction models in improving screening outcomes.

Guideline Central search terms used: PanCan model

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TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: (("lung cancer") AND ("pancan " AND "risk prediction" and "model") AND ("prevent" OR "screen" OR "early diagnos")) from_date:2013

A. Toumazis I, Bastani M, Han SS, Plevritis SK. Risk-Based lung cancer screening: A systematic review. Lung Cancer. 2020;147:154-186. doi:10.1016/j.lungcan.2020.07.007

B. Lam S, Bryant H, Donahoe L, et al. Management of screen-detected lung nodules: A Canadian partnership against cancer guidance document. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine. 2020;4(4):236-265. doi:10.1080/24745332.2020.1819175

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PLCOm2012 prediction model

Biomarker name: Revised Prostate, Lung, Colorectal, and Ovarian (PLCO) model for ever smokers made applicable to the National Lung Screening Trial (NLST) data (PLCOm2012) prediction model [A].

Biomarker context: Lung cancer screening using low dose computed tomography (LDCT) has been proposed as a tool to decrease lung cancer-specific mortality. The PLCOm2012 model estimates the 6-year lung cancer risk of ever-smokers aged 55-74 years by considering age, race/ethnicity, education status, BMI, COPD, personal history of cancer, family history of lung cancer, smoking status, smoking intensity measured in pack-years, and time since cessation as risk factors. It intends to identify those persons at higher risk of developing a lung cancer, which might benefit more from lung cancer screening using low dose computed tomography, improving the sensitivity and specificity of LDCT screening. The model was adapted from a previous one, developed in the Prostate, Lung, Colorectal, and Ovarian study (PLCO model for ever-smokers) to consider also the National Lung Screening Trial results. BMI is the only biomarker included in this prediction model.

Test definition: PLCOm2012 model to identify patients at high risk of lung cancer in ever-smoker adults for LDCT screening.

Results of the search

No results were identified in Guideline Central. The search terms yielded 2 results in the TRIP search, and only one matches the test definition.

Evidence of clinical utility of the test

Evidence 1: Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement [B].

The guidelines, has a TRIP score of 7 and were last revised in 2013, focus on the accuracy of LDCT for lung cancer screening, as well as the related benefits and hazards. They provide information on the ideal age range for screening beginning and ending, as well as suggested screening intervals. The guidelines also compare the relative advantages and disadvantages of different screening procedures to modified multivariate prediction models. According to the document, the USPSTF commissioned comparative modelling studies to explore screening benefits and hazards using risk prediction models in relation to age and smoking history. The PLCOm2012 was one of the models evaluated. It states that, while risk prediction algorithms expanded screening to older people, lowering lung cancer deaths, they also led to overdiagnosis at older ages, resulting in less years gained. Implementing advanced risk prediction models may hamper mass screening acceptance, and their performance is questionable when compared to age and smoking status. They reach the conclusion that using complicated risk prediction models for eligibility may present implementation challenges, and there is inadequate data to indicate their superiority over age and smoking history criteria in improving outcomes.

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Conclusion

In conclusion, there is no recommendation of the clinical utility of the model. Based on the guideline careful consideration and further evidence is needed to determine the clinical utility and effectiveness of complex prediction models in improving screening outcomes.

Guideline Central search terms used: PLCOm2012

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: (("lung cancer") AND ("PLCOm2012" AND "risk prediction" and "model") AND ("prevent" OR "screen" OR "early diagnos")) from_date:2013

A. Toumazis I, Bastani M, Han SS, Plevritis SK. Risk-Based lung cancer screening: A systematic review. Lung Cancer. 2020;147:154-186. doi:10.1016/j.lungcan.2020.07.007

B. US Preventive Services Task Force, Krist AH, Davidson KW, et al. Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2021;325(10):962. doi:10.1001/jama.2021.1117

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Prostate Health Index (PHI)

Biomarker name: Prostate Health Index (PHI) test [A].

Biomarker context: Prostate cancer screening with PSA has many limitations, and its clinical utility is still under debate. Researchers are looking for alternative biomarkers that may help to identify clinically relevant prostate cancer cases from those that will not become aggressive tumours. Prostate Health Index (PHI) is calculated with total Prostate-Specific Antigen (tPSA), free PSA (fPSA), and [-2]pro-PSA (p2PSA) using the following formula: (p2PSA/fPSA) x √tPSA. Its aim is to improve the prediction of the presence of prostate cancer and its aggressiveness in the context of prostate cancer screening relative to tPSA, fPSA, and PSA density alone. There is a commercially available U.S. Food and Drug Administration (FDA) approved test to measure PHI.

Test definition: the measurement of the PHI in blood using the combination of all three forms of PSA (total PSA, free PSA and p2PSA) for the improved screening of prostate cancer in the general male population.

Results of the search:

The search terms resulted in zero guidelines for the test definition in Guideline Central. The terms used in TRIP produced nineteen guidelines and only three matched the test definition. Eleven guidelines did not match the disease of interest, three were not focused on the specified prevention level and the remaining guidelines were repetitions or updates of previous guidelines, which did not match the test definition.

Evidence of clinical utility for the test

Evidence 1: PSA testing and early management of test-detected prostate cancer [B].

The guideline was published in January 2016 by the Cancer Council Australia in collaboration with The Prostate Cancer Foundation of Australia. The original country of publication is Australia. It has a TRIP score of 7.

This guideline makes recommendations on how best to support men in making an informed decision for or against PSA testing, including which testing protocol to recommend to men in favour of testing, depending on their age and underlying risk of prostate cancer. In relation to the PHI, the guideline recommends not to use PSA velocity or the PHI test as adjuncts to total PSA testing in determining whether or not to offer prostate biopsy, except in the context of research conducted to assess their utility for this purpose.

Evidence 2: 2022 Canadian Urological Association recommendations on prostate cancer screening and early diagnosis [C].

The guideline was published in April 2022 by the Canadian Urological Association. The original country of publication is Canada. It has a TRIP score of 6.

This document aims to provide guidance on the current best practice in prostate cancer screening, early diagnosis practices and to provide information on new and emerging diagnostic modalities. In the context of PHI, it highlights that in men with a moderately elevated PSA, PHI may improve the prediction of prostate cancer and provide additional

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information over PSA alone. However, it does not recommend the use of these tests, as they are not regarded as cost-effective.

Evidence 3: EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer [D].

This document was published in March 2023 by the European Association of Urology and is an update of the previous version published in 2022. It is endorsed by different European Urological, Radiography and Oncology organisations such as the European association of Nuclear Medicine, European Society of Urogenital Radiology or the European Society for Radiotherapy and Oncology. It has a TRIP score of 8.

This guideline document aims to assist medical professionals in the evidence-based management of prostate cancer in terms of screening, diagnosis and local treatment. It indicates that, in men with an elevated risk of PCa with a prior negative biopsy, the role of PHI in deciding whether to take a repeat biopsy is uncertain and probably not cost-effective.

Conclusion

The guidelines do not recommend using the PHI alongside PSA as a clinical test to improve screening of prostate cancer in men. There are multiple examples demonstrating research activity in PHI, which is promising however, at this stage the clinical utility is not seem to be cost-effective. Also, the use of MRI is likely to affect the clinical utility of above-mentioned biomarkers.

Guideline Central search terms used: Prostate Health Index

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: (("phi" OR "prostate health index") AND ("prostate cancer") AND ("prevent" OR "screen" OR "early diagnos"))from_date:2013

A. Agnello L, Vidali M, Giglio RV, et al. Prostate health index (PHI) as a reliable biomarker for prostate cancer: a systematic review and meta-analysis. *Clin Chem Lab Med*. 2022;60(8):1261-1277. doi:10.1515/cclm-2022-0354

B. Prostate Cancer Foundation of Australia CCA. PSA Testing and Early Management of Test detected Prostate Cancer- Clinical practice guidelines. *Prostate Cancer Found Aust Cancer Counc Aust*. Published online January 2016. https://www.racgp.org.au/clinical-resources/clinical-guidelines/guidelines-by-topic/endorsed-guidelines/clinical-practice-guidelines-psa-testing-early-man

C. Mason RJ, Marzouk K, Finelli A, et al. UPDATE – 2022 Canadian Urological Association recommendations on prostate cancer screening and early diagnosis: Endorsement of the 2021 Cancer Care Ontario guidelines on prostate multiparametric magnetic resonance imaging. *Can Urol Assoc J*. 2022;16(4):E184-96. doi:10.5489/cuaj.7851

D. Mottet N, P. Cornford, R.C.N. van den Bergh, et al. EAU - EANM - ESTRO ESUR - ISUP - SIOG Guidelines on Prostate Cancer. *Eur Assoc Urol*. Published online April 2023. https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2023_2023-03-27-131655_pdvy.pdf

PROPHET a PeRsOnalized Prevention roadmap for the future HEalThcare

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SelectMDx

Biomarker name: SelectMDx [A].

Biomarker context: Various molecular biomarker tests have been developed as diagnostic techniques for the early and non-invasive identification of prostate cancer (PCa). Urine collection is straightforward and prostate cells are discharged directly into the urethra following digital rectal examination (DRE), meaning the non-invasive detection of urine-related biomarkers has become a promising alternative screening technique and a research focus. Some innovative urine indicators, such as Progensa Prostate Cancer Antigen 3 (PCA3), SelectMDX, ExoDx Prostate Intelliscore (EPI), Mi-ProstateScore (MiPS), and others, have gradually been employed for prostate cancer monitoring and detection. SelectMDX is a urine test designed to assess the expression of two mRNA cancer-related biomarkers, related with distal-less homeobox 1 (DLX1) and homeobox C6 (HOXC6) genes.

Test definition: SelectMDX is a urine test that measures the expression of two mRNA cancer-related biomarkers and combines them with clinical risk factors (age, PSA, prostate volume, family history, digital rectal exam) to determine the risk of developing clinically significant prostate cancer in men.

Results of the search

Upon conducting a search in the TRIP database, we discovered four suitable documents, three of which were different versions of the same guideline. Among these options, we chose the most recent.

Evidence of clinical utility for the test

Evidence 1: EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer [B].

This document was published in March 2023 by the European Association of Urology and is an update of the previous version published in 2022. It is endorsed by different European Urological, Radiography and Oncology organisations such as the European association of Nuclear Medicine, European Society of Urogenital Radiology or the European Society for Radiotherapy and Oncology. It has a TRIP score of 8.

This guideline document aims to assist medical professionals in the evidence-based management of prostate cancer in terms of screening, diagnosis and local treatment. The guideline discusses that SelectMDX may help to prevent needless biopsies and exhibits a significant negative predictive value when used in conjunction with MRI, but its clinical added value is unclear within the framework of the existing practice of MRI followed by focused biopsies.

Evidence 2: Clinical Appropriateness Guidelines: Molecular Testing of Solid and Hematologic Tumors and Malignancies [C].

This guideline, with a TRIP score of 0, aims to assist medical professionals in the evidence-based management of prostate cancer in terms of screening, diagnosis and local treatment. It states that SelectMDx is deemed medically necessary for men aged 50 and above with a

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PSA level between 3.1 and 10.0 ng/mL who have not undergone recent treatment for BPH and have not used medications affecting PSA levels in the past six months.

Conclusions
Although SelectMDx has the potential to improve diagnostic decision-making and reduce the need for unnecessary biopsies, additional research and clinical evidence are required to determine its specific clinical benefits, particularly when compared to the current standard practise of using MRI and targeted biopsies as the initial diagnostic approach. Currently, there appears to be some indication of the clinical utility of the biomarker, although it is not yet definitive.

Guideline Central search terms used: selectmdx

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: (("prostate cancer") AND ("selectmdx") AND ("prevent" OR "screen" OR "early diagnos")) from_date:2013

A. Wang L, He W, Shi G, et al. Accuracy of novel urinary biomarker tests in the diagnosis of prostate cancer: A systematic review and network meta-analysis. *Front Oncol*. 2022;12:1048876. doi:10.3389/fonc.2022.1048876

B. Mottet N, P. Cornford, R.C.N. van den Bergh, et al. EAU - EANM - ESTRO ESUR - ISUP - SIOG Guidelines on Prostate Cancer. *Eur Assoc Urol*. Published online April 2023. https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2023_2023-03-27-131655_pdvy.pdf

C. Molecular Testing of Solid and Hematologic Tumors and Malignancies. *AIM Specialty Health*. Published online 2023. https://aimproviders.com/genetictesting/wp-content/uploads/sites/15/2022/03/GT04-Molecular-Testing-of-Solid-and-Hematologic-Tumors-v2.2022-FINAL.pdf

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a PeRsOnalized Prevention roadmap for the future HEalThcare
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3.1.4 Tests with no evidence – cancer

The test/biomarkers identified from Task 2.1.1 in which we could not find any type of evidence is presented in Table 3.1C. Many are still in the research phase and have not reached clinical implementation. The list also includes several lung cancer prediction models.

TABLE 3.1C: Tests with no evidence of clinical utility, cancer. Matching shaded rows indicate test definitions derived from the same paper. Reports available from the authors on request.

Test definition	Unique Biomarker Name
Genetic test identifying the inactive version of *ALDH-2* that significantly increases the risk of **gastric cancer** in moderate to heavy drinkers.	aldehyde dehydrogenase-2 (*ALDH2*) gene.
Bayesian Inference Malignancy Calculator (BIMC) model to estimate the probability of malignancy for screen-detected solitary pulmonary nodules in adult patients to improve **lung cancer** detection.	BIMC model.
Genetic test to identify a variant in the *CASP-9* gene that increases the risk of: 1. **all cancers** in a general population 2. **colorectal cancer** in an Asian population 3. **lung cancer** in an Asian population 4. **prostate cancer** in an Asian population.	caspase-9 (*CASP9*) gene.
Genetic test to identify variation in the 3' UTR of the *CD44* gene that alters miRNA binding in the general population indicating an increased risk of **colorectal cancer**.	*CD44* gene.
A genetic test to identify specific variants in the *CHRNA3* gene that increase the risk of **lung cancer** in: 1. European populations 2. Asian populations.	cholinergic receptor nicotinic alpha 3 (*CHRNA3*) gene.
Genetic test to identify variants in the *CHRNA5* gene which increase the risk of **lung cancer** in European populations.	cholinergic receptor nicotinic alpha 5 (*CHRNA5*) gene.
COPD-LUCSS + DLCO model to identify patients at high risk of **lung cancer** in adults for LDCT screening.	COPD-Lung Cancer Screening Score (COPD-LUCSS) using the diffusing capacity for carbon monoxide (DLCO) prediction model.

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Test definition	Unique Biomarker Name
The measurement of the levels of EBV-VCA IgA in serum to determine an individual's risk of developing **stomach cancer.**	EBV-VCA IgA (Immunoglobulin A antibodies against Epstein-Barr Virus Viral Capsid Antigen (VCA))
The measurement of the levels of EBV-VCA IgG in serum to determine an individual's risk of developing **stomach cancer.**	EBV-VCA IgG (Immunoglobulin G antibodies against Epstein-Barr Virus Viral Capsid Antigen (VCA))
The measurement of the levels of EBV-VCA IgM in serum to determine an individual's risk of developing **stomach cancer.**	EBV-VCA IgM (Immunoglobulin M antibodies against Epstein-Barr Virus Viral Capsid Antigen (VCA))
El-Zein model to identify patients at high risk of **lung cancer** in adults for LDCT screening.	El-Zein prediction model (Covidence ID: #49852).
Genetic test to identify variation in the 3' UTR of the *ERCC1* gene that alters miRNA binding in the general population to indicate an increased risk of **colorectal cancer**.	*ERCC1* gene
Etzel + 6 SNPs model to identify African American individuals at high risk of **lung cancer** death in adults for LDCT screening.	Modified Etzel model with addition of 6 SNPs prediction model
The measurement of folate levels in plasma, using a chemiluminescent immunoassay, to estimate the risk of developing **breast cancer** in women.	Folate or folic acid
Genetic test to identify a variant in *GPX4* which increases the risk of developing **colorectal cancer**.	Glutathione peroxidase 4 gene (*GPX4*)
A genetic test to identify a variant in the *HIF-1a* gene that significantly increases or decreases the risk of: 1. **all cancer** in a general population 2. **all cancers** in Asian populations 3. **lung cancer** 4. **pancreatic cancer** 5. **prostate cancer** 6. **gastrointestinal cancers**.	Hypoxia-inducible factor-1 (*HIF-1*) gene
Hoggart prediction model to identify patients at high risk of **lung cancer** in adults for LDCT screening.	Hoggart prediction model
Genetic test to identify a variant in the Long non-coding RNA (lncRNA) *HOTAIR* for increased risk of **lung cancer** in the general population.	lnc homeobox transcript antisense intergenic RNA (*HOTAIR*)
The measurement of the levels of total IgA in serum to determine an individual woman's risk of developing: 1. **breast cancer**	Total immunoglobulin A (IgA)

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a PeRsOnalized Prevention roadmap for the future HEalThcare
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Test definition	Unique Biomarker Name
2. **Lung cancer**	
The measurement of the levels of total IgE in serum to determine an individual male's risk of developing **prostate cancer.**	Total immunoglobulin E (IgE)
The measurement of the levels of allergen specific IgE in serum to determine a male's risk of developing **prostate cancer.**	Immunoglobulin E (IgE) – allergen specific
The measurement of the levels of asthma specific IgE in serum to determine an individual male's risk of developing **prostate cancer.**	Immunoglobulin E (IgE) – asthma specific
Genetic test to identify the *IGFBP1* gene indicating an increased risk of **colorectal cancer** in the general population.	Insulin-Like Growth Factor-2 Binding Protein-1 (*IGFBP1*) gene
Genetic test to identify a variant the *IL-10* gene that increases the risk of **prostate cancer** in a male Caucasian population.	Interleukin-10 (*IL-10*) gene
INTEGRAL + protein biomarker panel prediction model to identify patients at high risk of **lung cancer** in adults for LDCT screening.	Integrative Analysis of Lung Cancer Etiology and Risk (INTEGRAL) model using a panel of five protein biomarkers prediction model
Genetic test to identify variation in the *KRAS* gene in the general population to indicate an increased risk of **colorectal cancer**.	*KRAS* gene
LCRAT prediction model to identify patients at high risk of having **lung cancer** (incidence) in adults for LDCT screening.	Lung Cancer Risk Assessment Tool (LCRAT) prediction model
Li prediction model to identify patients at high risk of **lung cancer** in Han Chinese adults for LDCT screening.	Li prediction model
LLP + SEZ6L prediction model to identify patients at high risk of **lung cancer** in adults for LDCT screening.	Modified Liverpool Lung Project (LLP) model with addition of SEZ6L SNP (LLP + SEZ6L) prediction model
LLP + 3 SNPs prediction model to identify patients at high risk of **lung cancer** in adults for LDCT screening.	Modified Liverpool Lung Project (LLP) model with addition of 3 SNPs prediction model
A genetic test to identify a variant in the LncRNA *H19* gene that: 1. increases the risk of **all cancers** in a general population. 2. decreases the risk of **all cancers** in a general population.	Long-coding RNA (Lnc) *H19*

PROPHET a PeRsOnalized Prevention roadmap for the future HEalThcare
Funded by the European Union
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Test definition	Unique Biomarker Name
A genetic test to identify a variant in the lncRNA *H19* gene that increases: 3. the risk of **haematological cancer** in a general population**.** 4. the risk of **gastroenterological cancer** in a general population. 5. the risk of **oral squamous cell carcinoma** in a general population. 6. the risk of **lung cancer** in a general population. 7. the risk of **hepatocellular carcinoma** in a general population.	
A genetic test to identify a variant in the *LOX* gene that increases the risk of: 1. **lung cancer** in a general population 2. **gynaecological cancer** in a general population.	Lysyl oxidase (*LOX*) gene
A genetic test to identify a variant in the *MALAT1* LncRNA which increases the risk of all cancers: 1. in a general population 2. in an Asian population.	metastasis associated lung adenocarcinoma transcript 1 (*MALAT1*) long coding RNA (Lnc)
Mayo model to estimate the probability of **malignant lung cancer** in radiologically indeterminate solitary pulmonary nodules (SPNs).	Mayo model
The characterization of microbiota profiles in breast tissue and stool for the early diagnosis of **breast cancer** in the general female population.	Human gut microbiota/microbiome
The characterization of microbiota profiles in stool for the improved screening of **colorectal cancer** in the general population.	Human gut microbiota/microbiome
The measurement of microRNA-155 levels in plasma, blood, urine and breast tissue for the early detection of **breast cancer** in the general female population	microRNA-155/miRNA-155
A genetic test to identify a variant in the *MMP-2* gene which increases susceptibility to: 1. **prostate cancer** in Asian populations 2. **prostate cancer** in a general population 3. **lung cancer** in Asian populations 4. **lung cancer** in the general population	matrix metalloproteinase-2 (*MMP-2*) gene (Covidence ID: #46409).

PROPHET
a PeRsOnalized Prevention roadmap for the future HEalThcare
Funded by the European Union
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Test definition	Unique Biomarker Name
A genetic test to identify a variant in the *MMP-7* gene which increases susceptibility to: 1. **bladder cancer** in Asian populations 2. **bladder cancer** in a general population 3. **cervical cancer** in Asian populations 4. **colorectal cancer** in Asian populations 5. **colorectal cancer** in a general population.	matrix metalloproteinase-7 (*MMP7*) gene
The measurement of the blood biomarker of osteoprotegerin (OPG) in serum to estimate the risk of developing **breast cancer** in BRCA1/BRCA2 carrier women.	Osteoprotegerin (OPG)
PanCan model + FEV1% prediction model to identify patients at high risk of **lung cancer** in adults for LDCT screening.	Modified Pan-Canadian Early Detection of Lung Cancer Study (PanCan) model using the percent-expected-forced expiratory volume in 1 s (FEV1%)
Genetic test to identify variation in the PAUF gene that results in an increased risk of **colorectal cancer** in the general population	PAUF gene
The measurement of the levels of phosphorus in serum to estimate the risk of developing **prostate cancer** in the general male population.	Phosphorus/phosphate
Genetic test to identify variation in the *PIK3CA* gene indicating an increased risk of **colorectal cancer** in the Chinese population.	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) gene
Peking University People's Hospital (PKUPH) model to estimate the probability of **pulmonary malignancy** for screen-detected solidary pulmonary nodules in adult patients.	PKUPH model
PLCOall2014 prediction model to identify patients at high risk of **lung cancer** in adults for LDCT screening.	Modified PLCO model evaluated risks in general population (PLCOall2014) prediction model
PLCO prediction model to identify patients aged 55-74 years at high risk of **lung cancer** in adults for LDCT screening.	Prostate, Lung, Colorectal, and Ovarian (PLCO) prediction model
The measurement of PUFA levels in serum to estimate the risk of developing **colorectal cancer** in the general population.	n-3 Polyunsaturated Fatty Acids
Qian prediction model to identify patients at high risk of **lung cancer** in adults for LDCT screening.	Qian prediction model
Genetic test to identify variation in the *SMAD-7* gene to indicate an increased risk of **colorectal cancer** in a general population.	*SMAD-7* gene

PROPHET
a PeRsOnalized Prevention roadmap for the future HEalThcare
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UK participant in Horizon Europe Project PROPHET is supported by UKRI grant number 10040946 (Foundation for Genomics & Population Health)

Test definition	Unique Biomarker Name
The measurement of the increased levels of the blood biomarker soluble RANK ligand (sRANKL) in serum to estimate the risk of developing **breast cancer** in BRCA1/BRCA2 carrier women.	Soluble RANK ligand (sRANKL)
The Spitz prediction models to estimate the 1-year **lung cancer** incidence to identify: 1. Former smokers at high risk of **lung cancer** in adults for low dose computed tomography (LDCT) screening 2. Current smokers at high risk of **lung cancer** in adults for LDCT screening.	Spitz prediction models
A genetic test to identify a variant in *SOD2* that increases the risk of: 1. **urological cancer** in general populations 2. **urological cancer** in Caucasian populations 3. **prostate cancer** in a general population 4. **prostate cancer** in a Caucasian population.	superoxide dismutase-2 (*SOD2*)
TNSF-SQ prediction model to identify patients at high risk of **lung cancer** in non-smoking female adults for low dose computed tomography (LDCT) screening.	Taiwanese non-smoking female Lung Cancer Risk prediction models using genetic information and simplified questionnaire (TNSF-SQ)
Genetic test to identify variation in the *TGFBR1* gene miRNA binding site in the general population to indicate an increased risk of **colorectal cancer**.	*TGFBR1* gene
The measurement of trans fatty acids in serum to estimate the risk of developing **breast cancer** in postmenopausal women.	Trans fatty acid/ trans-fat
Veterans Affairs (VA) model to estimate the probability of **lung cancer** for screen-detected solidary pulmonary nodules in adult patients.	VA model
Wang prediction model to identify patients at high risk of **lung cancer** in adults for low dose computed tomography (LDCT) screening.	Wang prediction model
Ward + LCDRAT based prediction model including nicotine dependency to identify patients at high risk of **lung cancer** death in adults for LDCT screening.	Ward LCDRAT prediction model

PROPHET
a PeRsOnalized Prevention roadmap for the future HEalThcare
Funded by the European Union
UK participant in Horizon Europe Project PROPHET is supported by UKRI grant number 10040946 (Foundation for Genomics & Population Health)

Test definition	Unique Biomarker Name
Ward + LCRAT model to identify patients at high risk of **lung cancer** in ever-smoker adults for LDCT screening.	Ward LCRAT prediction model
Ward PLCOm2012 model to identify patients at high risk of **lung cancer** in ever-smoker adults aged 55-74 years for LDCT screening.	Ward PLCOm2012 prediction model
Weissfeld model to identify patients at high risk of **lung cancer** in ever-smoker adults for low dose computed tomography (LDCT) screening.	Weissfeld prediction model
Young prediction model to identify patients at high risk of **lung cancer** in adults for low dose computed tomography (LDCT) screening.	Young prediction model

PROPHET
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3.1.5 Genetic tests search results – cancer

A significant number of the papers with the highest level of evidence included genetic biomarkers, either alone or as part of other multivariate models. In the previous steps, we have searched for the genes mentioned in the papers but here we have reviewed genetics in the personalised prevention of cancer in a more general approach.

We conducted a search in the same databases, with the strategy outlined, to explore the state of evidence surrounding clinical utility of genetic testing for cancer.

We retrieved three guidelines that focused on overall cancer, five focused on breast cancer, one on prostate cancer, three on colorectal cancer, two on pancreatic cancer, two on corpus uteri cancer and two on kidney cancer. No results were identified for lung, stomach, liver, cervical or bladder cancer.

Biomarker name: Genetic testing

Biomarker context: Genetic testing in the context of cancer has emerged as a powerful tool for understanding and managing the disease. By examining an individual's genetic makeup, healthcare professionals can identify inherited mutations that may predispose them to certain types of cancer. This information might enable a more personalised approach to cancer prevention, diagnosis, and treatment. Genetic testing can provide insights into an individual's susceptibility, allowing personalised and proactive strategies to reduce or manage the risk of developing cancer. Individuals with identified genetic risks can undergo tailored screening programs and make informed decisions about proactive measures, such as lifestyle modifications or preventive surgeries, to mitigate their cancer risk.

Test definition: Genetic testing to analyse an individual's DNA to identify specific genetic variations, mutations, or biomarkers that may indicate an increased risk of developing certain cancers.

Results of the search:

The search in Guideline Central returned 65 results, but none were relevant to the test definition. The TRIP search resulted in 371 guidelines from which 18 matched the test definition.

Evidence of clinical utility for the test:

All cancers Evidence 1: Hereditary Cancer Testing [A]

This guideline was published in May 2023 by Carelon Medical Benefits Management. The country of publication is the United States.

The document seeks to assist providers in making the most appropriate treatment decision for a specific clinical condition for an individual. The guideline states that genetic testing is medically necessary under these criteria:

- The individual to be tested is either at significant risk for a genetic disorder (for example, based on family history) or suspected to have a known genetic condition
- Scientific literature has established that one or more genes have pathogenic variability associated with the genetic condition

PROPHET
a PeRsOnalized Prevention roadmap for the future HEalThcare
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UK participant in Horizon Europe Project PROPHET is supported by UKRI grant number 10040946 (Foundation for Genomics & Population Health)

- A biochemical or alternative test has been performed but the results are indeterminate, **OR** the genetic disorder cannot be identified through biochemical or other testing
- The genetic test has established clinical utility such that a positive or negative result of the genetic test will significantly impact clinical management and will likely result in a net improvement in health outcomes.

Evidence 2: Genetic testing in childhood. Guidance for clinical practice [B]

This report offers guidance to UK healthcare practitioners on genetic testing in children, discussing social and legal implications to encourage best practice. It explores different scenarios with regard to genetic testing for late-onset diseases, including tumours. In prenatal diagnosis, even though genetic testing is not usually offered for these diseases, it can be sometimes considered to inform the woman as she might modify her reproductive plans based on the test results (i.e., BRCA1/2). Conversely, after a child is born, there is a consensus that predictive genetic testing for late-onset disorders within the family should not be conducted unless it directly impacts the individual's health during childhood. This approach allows the people involved to make an informed decision about whether they want such information upon reaching adulthood.

The British Society for Genetic Medicine and the Royal College of General Practitioners both advise caution on Direct to Consumer genetic testing results, emphasising the importance of carefully considering the clinical utility of such tests and raising ethical concerns, particularly when applied to children.

Evidence 3: Genetic Testing for Hereditary Cancer Susceptibility [C]

This guideline was published in October 2022 by AIM Specialty Health. The country of publication is the United States.

The document addresses germline genetic testing for hereditary cancer predisposition syndromes. In relation with genetic testing, it states that genetic testing for hereditary cancer predisposition should be performed in genes with established evidence and clinical validity.

Evidence 4: Hereditary Cancer Syndromes and Risk Assessment [D]

This guideline was published in December 2019 by American College of Obstetricians and Gynecologists. The country of publication is the United States.

The document seeks to assist providers with recommendations regarding hereditary and ovarian cancer, cascade testing and referrals to genetics specialists. In relation to genetic testing the guideline recommends that, when necessary, genetic testing should be performed using a panel of multiple genes through next generation sequencing.

Breast cancer:

Evidence 5: Consensus Guideline on Genetic Testing for Hereditary Breast Cancer [E]

PROPHET a PeRsOnalized Prevention roadmap for the future HEalThcare
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The document was published in July 2019 by the American Society of Breast Surgeons. The country of publication is the United States.

This guideline outlines recommendations for genetic testing that medical professionals can use to assess hereditary risk for breast cancer in their patients. The guideline states that genetic testing should be made available to all patients with a personal history of breast cancer.

Evidence 6: Risk Assessment, Genetic Counselling, and Genetic Testing for BRCA-Related Cancer [F]

This document was published in November 2019 by the American Medical Association. The country of publication is the United States.

The objective of the guideline is to outline the recommendations on the risk assessment, genetic counselling, and genetic testing for BRCA-related cancer. In terms of genetic testing, the guideline states that women with BRCA1/2 gene mutations and with a positive result on the risk assessment tool should receive genetic counselling and, if indicated after counselling, genetic testing.

Evidence 7: Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer [G]

This document was originally published in June 2013 with the most recent update in November 2023 by the National Institute for Health and Care Excellence (NICE). The country of publication is the United Kingdom.

This guideline covers care for people with a family history of breast cancer and aims to improve the long-term health of these families by describing strategies to reduce the risk of and promote early detection of breast cancer, the treatment and surgery. Regarding genetic testing, the guideline states that genetic testing should be performed in family members if a high-risk predisposing gene mutation for breast cancer has been identified in the affected individual.

Evidence 8: Breast Cancer Risk Assessment and Screening in Average-Risk Women [H]

This document was published in July 2017 with an update in August 2023 by the American College of Obstetricians and Gynecologists (ACOG). The country of publication is the United States.

The guideline discusses breast cancer risk assessment, reviews breast cancer screening guidelines in average-risk women, outline controversies surrounding breast cancer screening and presents recommendations to assist women in making decisions surrounding breast cancer screening. It emphasises the relevance of risk assessment, especially with validated assessment tools (i.e. Gail, BRCAPRO, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, IBIS-Tyrer–Cuzick or Claus model). The assessment may include genetic testing, if desired, after appropriate counselling and informed consent is obtained.

Evidence 9: Evidence-based Guideline for the Early Detection, Diagnosis, Treatment and Follow-up of Breast Cancer [I]

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This document was published in May 2021 by the German Guideline Program in Oncology of the Association of The Scientific Medical Societies in Germany (AWMF), the German Cancer Society (DKG) and the German Cancer Aid Foundation (DKH). The country of publication is Germany.

In relation to genetic testing, the guideline states that genetic testing should be offered if there is a familial or individual exposure that is associated with at least a 10 % probability of mutation detection.

Prostate cancer

Evidence 10: EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer [J]

This document was published in March 2023 in France by the European Association of Urology and is an update of the previous version published in 2022. It is endorsed by different European Urological, Radiography and Oncology organisations such as the European association of Nuclear Medicine, European Society of Urogenital Radiology, European Society for Radiotherapy and Oncology.

This guideline document aims to assist medical professionals in the evidence-based management of prostate cancer in terms of screening, diagnosis, and local treatment. In relation to genetic testing, the guideline recommends germline testing in these scenarios:

- Men with high-risk PCa who have a family member diagnosed with PCa at age < 60 years.
- Men with multiple family members diagnosed with PCa at age < 60 years or a family member who died from PCa.
- Men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.

Colorectal cancer

Evidence 11: Clinical Practice Guideline on Screening for Colorectal Cancer in Individuals With a Family History of Nonhereditary Colorectal Cancer or Adenoma: The Canadian Association of Gastroenterology Banff Consensus [K]

This document was published in November 2018 by the Canadian Association of Gastroenterology. The country of publication is Canada. These consensus recommendations of this guideline aim to provide guidance on screening high-risk individuals for colorectal cancer. Regarding genetic testing, this guidelines states that germline genetic testing should be considered in those with a high burden of CRC among relatives.

Evidence 12: Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/ United Kingdom Cancer Genetics Group (UKCGG) [L]

This document was published in November 2019 by the British Society of Gastroenterology. The country of publication is the United Kingdom. The objective of this guidelines is to provide a clear strategy for the management of people at hereditary risk of colorectal cancer

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(CRC), which includes diagnosis, endoscopic management, prevention, and surgical care. In terms of genetic testing, this guideline recommends that patients should be referred to a specialist service which includes access to constitutional genetic testing in the presence of either deficient mismatch repair (MMR) or polyposis.

Evidence 13: Management of Colorectal Carcinoma [M]

This document was published in 2017 by the Ministry of Health of Malaysia in collaboration with the Malaysian Society of Colorectal Surgeons, the Malaysian Society of Gastroenterology and Hepatology, the Malaysian Oncological Society, and the Academy of Medicine Malaysia. The country of publication is Malaysia.The objective of the guideline is to provide evidence-based recommendations on colorectal carcinoma (CRC) surrounding the screening in average risk population, the surveillance of moderate and high-risk groups, the diagnosis and staging and the treatment and follow-up. In relation to genetic testing, it recommends that all individuals whose family history is suggestive of a hereditary colorectal cancer syndrome should be referred to a clinical genetic service for genetic risk assessment, where accessible.

Pancreatic cancer

Evidence 14: Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion [N]

This document was published in January 2019 by the American Society of Clinical Oncology. The country of publication is the United States. The guideline addresses how susceptibility to adenocarcinomas of the pancreas should be assessed, who should be genetically tested or screened for familial predisposition to pancreatic adenocarcinoma, and what pancreas surveillance strategies should be used in individuals with predisposition to pancreatic ductal adenocarcinoma. Regarding genetic testing, it recommends that individuals (cancer affected or unaffected) with a family history of pancreatic cancer meeting criteria for FPC, those with three or more diagnoses of pancreatic cancer in same side of the family, and individuals meeting criteria for other genetic syndromes associated with increased risk for pancreatic cancer have an increased risk for pancreatic cancer and are candidates for genetic testing.

Evidence 15: American Society for Gastrointestinal Endoscopy guideline on screening for pancreatic cancer in individuals with genetic susceptibility: methodology and review of evidence [O]

This document was published in February 2022 by the American Society for Gastrointestinal Endoscopy. The country of publication is the United States. The purpose of this guideline is to provide the best practice recommendations for pancreatic cancer screening in individuals at increased risk of pancreatic cancer because of genetic susceptibility. In terms of genetic testing, the guideline recommends universal genetic testing for all patients with pancreatic cancer regardless of family history because up to 50% of patients without a family history of pancreatic cancer have pancreatic cancer–predisposing mutations.

Endometrial cancer

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Evidence 16: Endometrial Cancer [P]

This document was published in September 2022 by the German Guideline Program in Oncology of the Association of The Scientific Medical Societies in Germany (AWMF), the German Cancer Society (DKG) and the German Cancer Aid Foundation (DKH). The country of publication is Germany.

The goal of this guideline is to inform and advise women about endometrial cancer diagnostics (clinical, imaging or surgical), the various therapeutic options (surgery, radiation, drug treatment) and their temporal and modular combinations in the different stages of the disease as well as the treatment of rare histological subtypes as well as hereditary variants. In terms of genetic testing, it states that if a causative genetic mutation is known in the family, the patient should inform the family members of the increased risk of endometrial cancer and explain the options for genetic counselling and (predictive) genetic testing.

Evidence 17: ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer Diagnosis, Treatment and Follow-up [Q]

This document was published in January 2016 by Elsevier Ireland on behalf of the European Society for Medical Oncology in collaboration with the European Society of Gynaecological Oncology and the European Society of Radiotherapy and Oncology.

The aim of this consensus conference was to produce multidisciplinary evidence-based guidelines on selected clinically relevant questions to complement the already-available European Society for Medical Oncology (ESMO) Clinical Practice Guidelines (CPG) for the diagnosis, treatment and follow-up of patients with endometrial cancer. Regarding genetic testing, the guideline recommends testing for hereditary nonpolyposis colorectal cancer (HNPCC)-associated genetic mutations, which is associated with a higher risk of endometrial cancer.

Kidney cancer

Evidence 18: Renal Mass and Localized Renal Cancer: Evaluation, Management, and Follow Up [R]

This document was published in May 2021 by the American Urological Association and presents an update of the 2017 publication Renal Mass and Localized Renal Cancer: AUA Guideline [S]. The country of publication is the United States.

This guideline summarises recommendations of the investigation, counselling and management of adult patients with clinically localised renal masses suspicious for cancer. In relation to genetic testing, the guideline states that clinicians should recommend genetic counselling for any of the following: all patients ≤ 46 years of age with renal malignancy, those with multifocal or bilateral renal masses, or whenever 1) the personal or family history suggests a familial renal neoplastic syndrome; 2) there is a first-or second-degree relative with a history of renal malignancy or a known clinical or genetic diagnosis of a familial renal neoplastic syndrome (even if kidney cancer has not been observed); *or* 3) the patient's pathology demonstrates histologic findings suggestive of such a syndrome.

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Evidence 19: European Association of Urology Guidelines on Renal Cell Carcinoma [T]

This document was published in March 2023 by the European Association of Urology and presents a substantial update of the 2022 publication. The original country of publication is the Netherlands. This guideline provides recommendations for urologists for the management of renal cancer. In terms of genetic testing, it strongly recommends performing a genetic evaluation in patients aged < 46 years, with bilateral or multifocal tumours and/or a first- or second-degree relative with RCC and/or a close blood relative with a known pathogenic variant and/or specific histologic characteristic that suggest the presence of a hereditary form of RCC.

No guidelines were identified for lung, stomach, liver, cervical or bladder cancer.

Conclusion of the genetic test search

The evidence found shows how for a range of cancers genetic testing is already incorporated in the clinical management of people who have high-risk germline mutations (i.e. familial cancers, multiple tumours, young cases). Some guidelines emphasise the ethical challenges associated with the use of these tests. Thus, these tests are considered to have clinical utility within the context of genetic counselling, where experts can provide the patient with information needed to interpret the results and make a decision regarding medical care (i.e. mastectomy in BRCA1/2 carriers). They also consider the family of the affected person and the cascade testing that may be required.

Search terms used for this biomarker:

Guideline Central search terms used: genetic test

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: (("cancer") AND ("genetic test") AND ("prevent" OR "screen" OR "early diagnos")) from_date:2013

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3.1.6 PRS search results – cancer

Non-monogenic complex diseases, such as the majority of tumour types, have a multifactorial aetiology. Typically, these conditions exhibit polygenic inheritance patterns influenced by a combination of genetic predisposition and environmental exposures. A PRS serves as an estimation of an individual's risk of developing a particular disorder, derived from the weighted correlations of single-nucleotide variants (previously known as single-nucleotide polymorphisms) or risk variants typically uncovered through genome-wide association studies [29]. Among the 57 papers with the highest evidence identified from Task 2.1.1, three focused on polygenic risk scores for cancer[A, B, C]. We conducted a targeted search specifically focusing on these types of biomarkers with the strategy outlined, to identify the evidence of their clinical utility.

We identified three guidelines that refer to cancer in general, usually as an example of complex chronic disease. Two focused on breast cancer, one on prostate cancer and one on liver cancer. No results were identified for lung, colorectal, stomach, pancreas, cervical, corpus uteri, kidney or bladder cancer.

Biomarker name: Polygenic risk scores (PRS) [A, B, C]

Biomarker context: Polygenic risk scores are widely promoted for their potential to play a substantial role in prevention, detection, and management of cancer. Cancer is a complex multifactorial disease, where genetic factors have an important contribution to its development. While some forms of cancer have a large hereditary component), in most tumours there is a combination of numerous genetic variables involved in its aetiology, each one with a minor impact. In cancer personalised prevention, a polygenic risk score (PRS) is a numerical representation of an individual's genetic predisposition for a tumour based on the combined impact of many genetic variations. These genetic variants, typically single nucleotide polymorphisms (SNPs), or changes at a single location in the DNA sequence, are given a weight based on how strongly they are linked to the tumour to provide a global risk score of the individual genetic susceptibility to the tumour [D].

Test definition: Use of PRS to identify a person's risk of developing cancer.

Results of the search: The search in Guideline Central returned three results, but none were relevant to the test definition. The TRIP search resulted in 70 guidelines where nine were relevant to the test definition. They are presented sorted by tumour location.

Evidence of clinical utility for the test

Evidence 1: The clinical application of polygenic risk scores: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG) [E]

This document was originally published in 2023 in the United States of America by the American College of Medical Genetics and Genomics. The document discusses some points on PRS and its clinical applications in relation to complex disorders, including cancer, and its aim is to "offer guidance to the health care provider who seeks to understand the challenges and limitations of applying PRS testing in patient care".

It is accompanied by a laboratory-oriented guideline that provides a complementary point of view on this issue [29]. The selected guideline states that clinical guidelines for the use of

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PRS in healthcare are currently lacking, emphasising that PRS offer probabilities rather than absolute disease risk, unlike specific genetic variants, and should be considered as a supplementary tool to assess the relative risk of developing a disorder. It also indicates that further research through prospective studies is essential to evaluate whether combining PRS results with preventive measures improves clinical outcomes. Its position is summarised in the following statements:

1. PRS test results do not provide a diagnosis, instead they provide a statistical prediction of increased clinical risk.
2. A low PRS does not rule out significant risk for the disease or condition in question.
3. If the risk prediction of a PRS is derived from a population that is different from the patient being tested, then the results may have a poor predictive value for the patient
4. Isolated PRS testing is not the appropriate test for clinical scenarios in which monogenic etiology is known or suspected
5. Before testing, a patient and provider should discuss the indications for the PRS test, and the patient should be informed how the PRS results will be used to guide medical management
6. PRS-based medical management should be evidence-based; however, there is currently limited evidence to support the use of PRS to guide medical management
7. Clinical follow-up for PRS should be consistent with best practices outlined by professional societies with appropriate expertise in instances when and where evidence-based practice guidelines exist
8. The ACMG's position is that preimplantation PRS testing is not yet appropriate for clinical use and should not be offered at this time.

It finally recommends: "At this time, the ACMG advocates against clinical implementation of PRS testing unless the provider and patient have a clear understanding of the limitations of the testing and applicability to the specific patient, including how the results will be used to guide evidence-based clinical care."

Evidence 2: Genetic testing in childhood. Guidance for clinical practice [F]

This report offers guidance to UK healthcare practitioners on genetic testing in children, discussing social and legal implications in order to encourage best practice. It explores different scenarios with regard to genetic testing for late-onset diseases, including tumours. With regard to polygenic risk scores, it remains uncertain whether some useful clinical applications will emerge for the modest shifts in risk estimates that they can generate for complex diseases, given the low fraction of disease heritability that they can explain. The guideline affirms that PRS have little or no demonstrated clinical utility and so would often be regarded as illegitimate in a healthcare context, especially for pre-implantation or prenatal testing of fetal polygenic risks.

Evidence 3: Carelon Clinical Appropriateness Guidelines: Appropriate Use Criteria: Polygenic Risk Scores in Genetic Testing [G]

The guidelines are specifically focused on the use of genetic testing for the application of polygenic scores in the context of complex traits and diseases such as cancer. The guide

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states that: “PRS is not ready for clinical implementation currently, but large clinical trials are underway to evaluate the clinical utility of various PRSs”.

Breast cancer:

Evidence 4: Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline [H]

This guideline published by the European Society of Medical Oncology (ESMO) offers suggestions for minimising risks and conducting screenings in individuals with a hereditary predisposition to breast and ovarian cancer. More specific to PRS, it states that validated risk assessment tools such as CanRisk (https://www.canrisk.org/), which uses the BOADICEA v6 model to calculate breast and ovarian cancer risks based on information entered for the individual which can include personal risk factors, cancer family history, genetic testing for high- and moderate-risk genes, polygenic scores and mammographic density, may be used to aid individual risk management. Finally, it also recommends that use of PRSs and other risk-reduction strategies should continue to be carried out and assessed in the context of clinical trials.

Evidence 5: Management of individuals with germline variants in PALB2: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG) [I]

The guideline seeks to provide guidance on personalised risk estimation for PALB2 germline pathogenic variant carriers, since it is associated with increased breast cancer risk. ACMG recommends the use of personalised risk estimates (e.g., CanRisk) in guiding clinical management.

The guideline includes a succinct general overview of PRS use in breast cancer, highlighting that most of the data correspond to populations of European ancestry (the ability to extrapolate to other populations is unclear). It discusses available data that suggest that PRS may be relevant as a modifier of the risk conferred by PALB2, combined with mammographic density and lifestyle/hormonal risk variables, allowing to further stratify these patients according to their risk of breast cancer. The guideline suggests that if and when PRS becomes available in the clinical setting, the afore mentioned integrated approach could be implemented in some online assessment tools such as CanRisk, although more data is needed to verify their efficacy in improving patient outcomes.

Prostate cancer:

Evidence 6: EAU - EANM - ESTRO ESUR - ISUP - SIOG Guidelines on Prostate Cancer. European Association of Urology [J]

The guideline discusses the use of PRS in a risk assessment tool only within the Stockholm3 test (which combines measurement of prostate-specific antigen (PSA), protein biomarkers, PRS -based on 232 SNPs-- and clinical information collected using a questionnaire, including age, family history, and previous prostate biopsies). It indicates that this test might help reduce the proportion of clinically insignificant cancers detected when used in combination with MRI in a PSA screening population (see section 3.1.2, Stockholm3 test).

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Liver cancer:

Evidence 7: Updated S2k Clinical Practice Guideline on Non-alcoholic Fatty Liver Disease (NAFLD) issued by the German Society of Gastroenterology, Digestive and Metabolic Diseases (DGVS) [K]

The purpose of the guideline is to offer guidance on the diagnosis, management, and monitoring of individuals with NAFLD, encompassing lifestyle changes and treatment. Nevertheless, it mentions a study of patient cohorts from Italy, Germany and the UK Biobank that showed that polygenic risk assessments based on the existence of risk variants might allow to stratify NAFLD patients regarding their liver cancer risk. However, the guideline does not offer a specific recommendation for the use of PRS in this context.

No guidelines were identified for lung, colorectal, stomach, pancreas, cervical, corpus uteri, kidney or bladder cancer.

Conclusion

In conclusion, for those cancers with guidelines that address PRS (breast, prostate, and liver), they are not yet recommended as risk-assessment tools in clinical practice. PRSs are being evaluated mostly in the context of screening, as a standalone test or in combination with other tests and epidemiological data, or as an additional instrument to better classify the risk among those with germline high-risk mutations. Major determinants of the clinical utility of PRSs in the future will be their cost (genotyping and risk scoring) and their ability to differentiate individuals based on risk. Patients will also need clear information to understand and interpret the information the scores may provide.

Guideline Central search terms used: polygenic

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: (("cancer") AND ("polygenic") AND ("prevent" OR "screen" OR "early diagnos")) from_date:2013

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K. F. Tacke, A. Canbay, H. Bantel, et al. Updated S2k Clinical Practice Guideline on Non-alcoholic Fatty Liver Disease (NAFLD) issued by the German Society of Gastroenterology, Digestive and Metabolic Diseases (DGVS) – April 2022 – AWMF Registration No.: 021–025. Z Für Gastroenterol. 2022;60(09):e733-e801. doi:10.1055/a-1880-2388

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3.1.7 Cancer discussion

While considerable advances have been made in the identification and assessment of cancer biomarkers for prevention, our results show that evidence of their clinical utility is, in many cases, limited. Translation of a biomarker discovery into a valuable test is a challenging process.

Test definition has been crucial for the successful completion of this phase of the project. However, this has been challenging due to the complex nature of some of the biomarkers, which, in some cases, has made it impossible to produce a definition of the test for the search (i.e. multivariate models). When the use of the biomarker changed by disease type or population it created additional test definitions which were grouped in the same write-up.

For cancer, among the 57 papers with the highest level of evidence, we identified 82 unique biomarkers with 113 test definitions which were used to assess their clinical utility. A number of other biomarkers were excluded as in the original paper they did not show a significant association with the disease of interest or did not allow us to establish appropriate test definitions.

The papers with the highest evidence were concentrated in the most frequent and deadly tumours, mainly breast cancer, prostate cancer, liver cancer and gastric cancer, followed by colorectal cancer, lung cancer, pancreatic cancer, and cervical cancer. There were no biomarkers for cancers of the corpus uteri, kidney or bladder. This reflects the results that were obtained from Task 2.1.1, where breast, prostate, lung and colorectal type of cancers were the focus of research in more than two thirds of the papers, while corpus uteri, kidney and bladder cancers had the fewest studies.

Among those included, most of the papers focused on genetic biomarkers (genes and single nucleotide polymorphisms [SNPs]). The other biomarkers that appeared in the selected papers were mainly biochemical, either alone or in models combined with other personal or clinical data, and in some cases (lung or breast cancer) with imaging biomarkers. Several predictive models evaluated included BMI as the only biomarker. In contrast, epigenetic or other categories of biomarkers were not identified in any of the prioritised papers.

Most of the tests with evidence of clinical utility were multivariate predictive models (i.e. Tyrer-Cuzick model for breast cancer, Stockholm test for prostate cancer or the Galad Score for liver cancer). Other tests with evidence included those improving the screening of breast cancer by combining breast density, digital breast tomosynthesis and two-dimensional mammography and estimating the risk of developing prostate cancer and colorectal cancer by identifying mutations and germline pathogenic variants in key genes.

In terms of the level of prevention, those tests that evaluated prospective risk of developing a tumour can be applied for both primary and secondary prevention purposes. Other tests tried to improve the performance of the screening programs for these diseases. Nevertheless, in many cases, papers did not always clearly define it was difficult to establish a difference between risk models used to personalise strategies for secondary prevention (i.e. screening), to help to improve early diagnosis or to classify the progression of some lesions found to be clinically significant cancer, especially in the case of prostate cancer.

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Several risk prediction models for lung cancer screening have appeared in recent years, with some evidence suggesting that they outperform existing recommendations. Integrating these risk prediction models into screening programs has the potential to reduce lung cancer mortality while also reducing the requirement for unnecessary invasive follow-up treatments, hence increasing screening efficiency and cost effectiveness. Nonetheless, implementation studies are needed to identify hurdles to the adoption of risk-based screening programs. Before widespread deployment, the data required for these prediction models must be thoroughly evaluated, as well as the clinical practicality of each model.

Regarding genetic biomarkers in cancer, in our search of individual biomarkers we identified a number of genes related to familial cancer with evidence of clinical utility for prostate and colorectal cancer, as part of a multi-gene panel restricted to people with high risk or familial history of the disease. Our search for genetic testing also supported this approach. In several cancers, the evidence found shows how genetic testing has been already incorporated in the clinical management of those persons in which there is a high suspicion of probability of having high-risk germline mutations (i.e. familial cancers, multiple tumours, young cases). The use of these tests is recommended within the context of genetic counselling, where experts can provide the individual with the information needed to be able decide whether they want to have this test, to interpret the results and to decide whether they want to take any clinical or personal decision afterwards (i.e. mastectomy and oophorectomies in BRCA1/2 carriers). It also considers the family of the affected person and the cascade testing that may be offered. Thus, while testing for high-risk variants associated with familial risk or to specific syndromes, according to the guidelines found, this has clear clinical utility and is recommended in clinical practice together with genetic counselling. None of the guidelines established the clinical utility of genetic testing in the general population for personalised prevention of cancer.

With regard to PRS, our results do not support their clinical utility for cancer prevention at this stage. Disease specific PRS are generally recognised as potentially valuable biomarkers for informing clinical decisions, as they might improve risk prediction across cancer types and clinical contexts. However, their broad adoption in clinical practice requires a thorough understanding of their implications and demands on the health care system, as well as on the information they provide and a clear definition of the appropriate context of use. Furthermore, ongoing efforts are essential for accumulating enough evidence to assess their clinical utility and to support implementation initiatives. Premature use of polygenic scores in cancer risk assessment could damage these efforts and weaken trust in this promising approach to improving population health.

In conclusion, we identified a small number of tests with clinical utility for the prevention of cancer. The tests with evidence included models that add biomarkers to personal and clinical data to stratify individuals into risk groups.

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3.2 Cardiovascular diseases

Any assessment of clinical utility requires a certain level of scientific evidence and biomarkers most likely to have some degree of evidence to support a clinical utility assessment were short-listed by filtering our results based on the study design. The papers identified in the scoping review with the study design of meta-analyses, randomised control trials and review (systematic, scoping, and umbrella) were included in Task 2.1.2. The biomarkers from these papers formed the prioritised biomarkers list. Prioritisation of CVD papers identified in Task 2.1.1 resulted in the identification of 47 papers (Table 3.2A).

TABLE 3.2A. The number of papers identified as having biomarkers for prevention of CVD identified in the scoping review and following prioritisation for Task 2.1.2.

Total number of papers identified in the scoping review	775
Systematic review and meta-analysis papers	23
Review papers	7
RCT papers	17
Prioritised papers for review	**47**

3.2.1 Development of test definitions in CVD

Key to this search strategy is defining the test that uses the biomarker of interest. Through this process 24 papers and their biomarkers were excluded. There were several reasons for this, such as the outcome of the study being that there is no association with the disease of interest. In some cases, whilst biomarkers fit the criteria for evaluation in Task 2.1.1, they did not meet the criteria for evaluation in Task 2.1.2 because a test could not be defined. This was frequently due to biomarkers identified in review cases where the potential of the marker was examined but how it would be used clinically was not addressed. In some cases, a test definition could be determined that encompassed multiple Task 2.1.1 papers for the same biomarker. Multiple test definitions using the same biomarker could also be combined into the same report in cases where only the population, disease of interest or sample type changed between the papers. For example, multiple test definitions were included in the report for 'retinal vascular calibre' (Table 3.2B). The screening process remained the same but could be used in the detection of both coronary artery disease and stroke.

Within CVD we began our evaluation with 58 individual test definitions from 23 papers which covered multiple CVD groups with stroke, specifically ischemic stroke, being the most frequent group investigated. Each test definition covering a biomarker was subject to our search strategy.

From the searches we have produced eight reports for tests which had evidence of clinical utility (Table 3.2B). Twenty-three (comprising 17 reports) tests did not have any evidence of clinical utility (Table 3.2C).

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3.2.2 Tests with evidence of clinical utility – CVD

Following the search strategy an individual report for each test definition was produced based on the results of the search conducted. This report includes context for the biomarker's use, the test definition and the findings of the search. A conclusion summarising the findings is provided. The search terms used for each database can be found in each individual report along with references to the evidence identified.

From the searches we have produced eight reports for tests which had evidence for clinical utility (Table 3.2B).

TABLE 3.2B. Tests with evidence of clinical utility including biomarker details for CVD. Matching shaded rows and paper references included to indicate test definitions derived from the same paper.

Test	Biomarker
Evidence of clinical utility	
CAC scores to identify people at risk of developing cardiovascular disease (CVD) in a general population	Coronary Artery Calcium (CAC) score. Van Der Aalst CM, Denissen SJAM, Vonder M, et al. European Heart Journal - Cardiovascular Imaging. 2020;21(11):1216-1224. doi:10.1093/ehjci/jeaa168; Nassar M, Nso N, Emmanuel K, et al. Coronary Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2022;16(6):102503. doi:10.1016/j.dsx.2022.102503
CAC scores to identify type 2 Diabetes Mellitus (T2DM) patients at high risk of major CVD events	
Use of a doppler ultrasound to detect atheroma or atherosclerosis and identify people at increased risk of CVD	Carotid atherosclerosis; calcified carotid artery atheroma. Mupparapu M, Abomr D, Nath S. QUINTESSENCE INTERNATIONAL. 2021;52(4).
Blood test for APOA1 for early-stage screening in suspected patients of ischaemic stroke	Apolipoprotein A1 (APOA1) Jadav RK, Mortazavi R, Yee KC. J Clin Med. 2022;11(14):4243. doi:10.3390/jcm11144243
CHARGE-AF Prediction Model for primary screening of atrial fibrillation (AF) in adults	Cohorts for Heart and Aging Research in Genomic Epidemiology model for AF (CHARGE-AF) prediction model. Himmelreich JCL, Veelers L, Lucassen WAM, et al.Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol. 2020;22(5):684-694. doi:10.1093/europace/euaa005
CHARGE-AF Prediction Model for primary screening of AF in patients above the age of 65 years	
RECODe to identify T2DM patients at risk of myocardial infarction (MI) later in life	The Risk Equations for Complications of Type 2 Diabetes (RECODe) score. Buchan TA, Malik A, Chan C, et al. Heart. 2021;107(24):1962-1973. doi:10.1136/heartjnl-2021-319243
RECODe to identify T2DM patients at risk of stroke later in life	

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In the case of tests with evidence regarding their clinical utility two cases considered multi-factorial models comprising physiological and biochemical biomarkers such as blood pressure or serum creatinine and additional health data including CVD history, height, weight and prescribed medication. Guidelines were identified supporting the use of both the CHARGE-AF model to predict risk of atrial fibrillation and RECODe which predicted risk of CVD events later in life in diabetic patients. Both models incorporate previously validated methods of assessing CVD risks, therefore the availability of guidelines supporting their use suggests that combining these risk factors into a single model produces a robust assessment of longer-term CVD risk.

Further examples of tests with evidence of clinical utility appear to be associated with already established assays and procedures such as assessment of coronary artery calcification (CAC) or measurement of apolipoprotein A. The broad utility of these techniques is not in question however adjusting their use case for a different population or disease outcome is being investigated in multiple areas.

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Coronary Artery Calcium (CAC) score

Biomarker name: Coronary Artery Calcium (CAC) score [A] and [B]

Biomarker context 1: Evidence shows that CAC scores are strong independent predictors of cardiovascular disease (CVD) events which may improve risk classification in patients, leading to earlier preventive treatment or reclassification to low risk thus reducing health care burdens.

Test definition 1: CAC scores to identify people at risk of developing cardiovascular disease (CVD) in a general population.

Biomarker context 2: Patients with type-2 diabetes mellitus (T2DM) are at a high risk of developing CVD however none of the routinely available screening methods provide conclusive results for T2DM patients. CAC scoring may provide an appropriate method to investigate atherosclerosis and predict CVD events in people with T2DM.

Test definition 2: CAC scores to identify T2DM patients at high risk of major CVD events.

Results of the search: Guideline Central results produced two documents, one of which was relevant to test definition 1. Of the nine documents identified in the TRIP search we found that two were suitable for use with our test definition.

Evidence of clinical utility for the test

Test definition 1: CAC scores are rapid and non-invasive and can be used to identify people at risk of developing CVD in a general population.

Evidence 1: The National Lipid Association scientific statement on coronary artery calcium scoring to guide preventive strategies for ASCVD risk reduction [C].

This document was published in December 2020 by an Expert Panel of The National Lipid Association. The statement reviews evidence for the use of CAC scores in different patient populations to guide preventive strategies for atherosclerotic cardiovascular disease (ASCVD) risk reduction. It provides updates to the evidence-based appropriate use of CAC scoring along with clinical recommendations in the context of a patient's 10-year ASCVD risk. Several recommendations are made.

The statement advises that CAC score reports should include both the absolute Agatston CAC score, which is the best predictor of absolute 5-to-10-year ASCVD event risk and the age, sex, and ethnicity-based CAC percentiles which best predicts relative risk, lifetime risk trajectory and lifetime treatment benefit.

Different recommendations depending on the age and health status of a patient are also made. For example, CAC scoring is advised in patients 40-75 years of age, with low-density lipoprotein cholesterol (LDL-C) measurement of 70-189mg/dL (milligrams per 100 millilitres) and a 10-year ASCVD of 5-19% to decide on the need for, and intensity of preventive therapies.

The statement also addresses the utility of CAC scoring when different ethnicities or genders are considered. It advises that CAC scoring for ASCVD risk assessment should be used regardless of ethnicity or gender.

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A CAC score of 0 is seen as the single strongest negative predictor for developing a cardiovascular event. Therefore, it is advised that in adults aged 40-75 years with a low-density lipoprotein cholesterol (LDL-C) of 70-189 mg/dL and without diabetes, active cigarette smoking or a family history of premature ASCVD and a CAC score of 0 it is reasonable to defer statin initiation.

Several other recommendations are found within the document which relate to disease management rather than prevention.

This statement concludes that CAC scoring is a widely available, safe, cost-effective, and rapidly performed test that improves discrimination of those at risk for ASCVD and serves to better reclassify risk, when used in conjunction with global risk scoring systems, than other clinically available tools.

Evidence 2: Non-invasive imaging in Coronary Syndromes: Recommendations of The European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE), in Collaboration with The American Society of Nuclear Cardiology, Society of Cardiovascular Computed Tomography (CT), and Society for Cardiovascular Magnetic Resonance [D].

These recommendations were published in April 2022 by the Journal of the American Society of Echocardiography. It was written as part of an international collaboration between those named in the title, all of whom approved the final version.

CAC scoring is described in the context of non-contrast CT study of the heart. It identifies that the CAC scoring system itself is a proven method for determining overall coronary atherosclerosis burden and has consistently been shown to be excellent for long-term (>10 years) risk prediction of adverse events in asymptomatic individuals.

Evidence 3: American College of Radiology (ACR) Appropriateness Criteria® Asymptomatic Patient at Risk for Coronary Artery Disease [E].

This document was revised in 2020, following publication in 2014 and published as part of the ACR Appropriateness Criteria series. The document highlights the ability of the CAC score as being the strongest known imaging predictor of CVD risk in asymptomatic patients. However, it then identifies that there is no relevant literature supporting the use of coronary CTA in asymptomatic patients at low risk of CAD. Supporting evidence was found for the use of coronary CTA in patients with intermediate risk caused by factors including metabolic syndrome, chronic inflammatory disorders or high-risk ethnic groups (e.g. South Asian) improved risk stratification. Use of CAC score in asymptomatic patients at high-risk of CAD was also recommended with the addition of intravenous (IV) contrast. To summarise, CAC scores were found to be appropriate in asymptomatic patients with intermediate or high-risk of CAD but not in low risk patients.

Conclusion for test definition 1

The guidelines highlight the utility of CAC scores as a method to identify long-term risk of CVD events, especially in asymptomatic patients with intermediate to high risk of CVD. Evidence document 1 also includes recommendations from multiple other sources indicating that the clinical utility of this biomarker in a general population has been established.

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Biomarker name: Coronary Artery Calcium (CAC) score [A] and [B].

Biomarker context 2: Patients with type-2 diabetes mellitus (T2DM) are at a high risk of developing CVD however none of the routinely available screening methods provide conclusive results for T2DM patients. CAC scoring may provide an appropriate method to investigate atherosclerosis and predict CVD events in people with T2DM.

Test definition 2: CAC score can be used to identify T2DM patients at high risk of major CVD events.

Results of the search: In Guideline Central the search terms identified one guideline that may have been relevant, 'The Obesity Algorithm' provides 'Important Principles for the Effective Treatment of Patients with Obesity' which is likely to include diabetic patients. However, it was behind a paywall and inaccessible therefore we could not confirm if a diabetic population was considered.

Within TRIP the initial search produced 72 guidelines which narrowed to 58 when we focussed on 2018 onwards. Many guidelines referred to CVD risk management however only one considered CAC scores within a diabetic population. The document identified above as **Evidence 3** placed the asymptomatic diabetic population within the 'asymptomatic but at high-risk' group meaning the use of CAC scoring, potentially with the addition of IV contrast, was recommended during CVD risk stratification in this population.

One additional 'scientific statement' document by Joseph *et al.* [F] highlighted that increasing CAC scores predicted MI and CV events after controlling for glycaemic control. It also identified that the Multi-Ethnic Study of Atherosclerosis (MESA) – Heinz Nixdorf Recall study (HNR) score which included CAC scores performed better in diabetic populations than Framingham and UK Prospective Diabetes Study (UKPDS) risk management tools.

No HTA or CEA documents relevant to the test definition were identified in TRIP. Five HTAs were identified through CRD however none covered the diabetic population and the majority covered computed tomography (CT) in screening for CAD.

Conclusion for test definition 2

We found one recommendation for the use of CAC scoring in diabetic populations and a scientific statement from Joseph *et al.* which highlighted the utility of CAC scores in diabetic patients. Therefore, we conclude that CAC scoring is a well-established tool for CVD screening in a general population and its use in diabetic populations is being established.

Search terms used for this biomarker **Test Definition 1:**

Guideline Central search terms used: coronary artery calcification score

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: cardiovascular disease

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: coronary artery calcification score

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Search terms used for this biomarker **Test Definition 2:**

Guideline Central search terms used: coronary artery calcification diabetic

Additional search parameters (or filters) used: coronary artery calcification diabetes

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: coronary artery disease diabetes

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: coronary artery calcification

Filtered to 2018 onwards

A. Van Der Aalst CM, Denissen SJAM, Vonder M, et al. Screening for cardiovascular disease risk using traditional risk factor assessment or coronary artery calcium scoring: the ROBINSCA trial. *European Heart Journal - Cardiovascular Imaging*. 2020;21(11):1216-1224. doi:10.1093/ehjci/jeaa168

B. Nassar M, Nso N, Emmanuel K, Alshamam M, Munira MS, Misra A. Coronary Artery Calcium Score directed risk stratification of patients with Type-2 diabetes mellitus. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2022;16(6):102503. doi:10.1016/j.dsx.2022.102503

C. Orringer CE, Blaha MJ, Blankstein R, et al. The National Lipid Association scientific statement on coronary artery calcium scoring to guide preventive strategies for ASCVD risk reduction. *Journal of Clinical Lipidology*. 2021;15(1):33-60. doi:10.1016/j.jacl.2020.12.005

D. Edvardsen T, Asch FM, Davidson B, et al. Non-Invasive Imaging in Coronary Syndromes: Recommendations of The European Association of Cardiovascular Imaging and the American Society of Echocardiography, in Collaboration with The American Society of Nuclear Cardiology, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *Journal of the American Society of Echocardiography*. 2022;35(4):329-354. doi:10.1016/j.echo.2021.12.012

E. Expert Panel on Cardiac Imaging: Ghoshhajra BB, Hedgire SS, Hurwitz Koweek LM, et al. American College of Radiology ACR Appropriateness Criteria: Asymptomatic Patient at Risk for Coronary Artery Disease: 2021 Update. *Journal of the American College of Radiology.* 2021:18(5):S2-S12. https://doi.org/10.1016/j.jacr.2021.01.003

F. Joseph JJ, Deedwania P, Acharya T, et al. Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes: A Scientific Statement From the American Heart Association. *Circulation*. 2022;145(9):e722-e759. doi:10.1161/CIR.0000000000001040

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Carotid atherosclerosis

Biomarker name: carotid atherosclerosis; calcified carotid artery atheroma [A].

Biomarker context: atherosclerosis can be measured to determine a person's risk of atherosclerotic cardiovascular diseases (CVD) events such as heart attack and stroke.

Test definition 1: Use of a doppler ultrasound to detect atheroma or atherosclerosis and identify people at increased risk of CVD.

Test definition 2: Use of panoramic radiography to detect atheroma or atherosclerosis and identify people at increased risk of CVD.

Results of the search: The search terms returned six guidelines in Guideline Central when we used the term 'carotid atherosclerosis', of which one was relevant to our test definition. The guidelines we did not select concentrated on the management of CVD such as ischemic stroke, aortic disease and peripheral artery disease rather than our focus of improved detection. No results were found for test definition 2 for guidelines or HTA and CEA documents.

Evidence of clinical utility for the test

Evidence 1: Assessment of Carotid Plaque by Ultrasound for the Characterization of Atherosclerosis and Evaluation of Cardiovascular Risk [B].

The document was published in July 2020 by The American Society of Echocardiography and endorsed by 23 different international Echocardiography and Cardiovascular imaging organisations including the Asian-Pacific Association of Echocardiography, the Chinese Society of Echocardiography, and the Italian Association of Cardiothoracic Anaesthesiologists. The original country of publication is the United States of America and it is relevant to **Test definition 1.**

The guideline provides a framework for enhanced cardiovascular risk stratification using plaque grading by 2-dimensional (2D) or 3-dimensional (3D) ultrasound. This has been produced to facilitate comparisons across studies and to improve patient stratification and monitoring. In the case of asymptomatic patients suspected to be at risk of atheroma and atherosclerosis the guidelines suggest a stepwise approach to CVD risk stratification. This begins with plaque visualisation via focussed carotid vascular ultrasound followed by 2D or 3D plaque quantification. In patients with symptoms suspicious of CVD, carotid ultrasound combined with functional stress testing is recommended. This combination is also likely to improve prognostic predictions of the development of CVD events and identify people who may benefit from aggressive medical intervention.

Conclusion

The guideline is highly supportive of the use of ultrasound **(Test definition 1)** to visualise and assess carotid arterial plaque during investigative pathways. Carotid focussed ultrasound provides the baseline information with which clinicians can then apply the plaque grading framework to allow improved risk stratification of their patients. The ultrasound portion of the test definition is recommended for clinical use, however the panoramic radiography **(Test definition 2)** is not addressed in this guideline.

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Search terms used for this biomarker

Guideline Central search terms used: calcified carotid artery atheroma; carotid atherosclerosis

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: cardiovascular disease

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: calcified carotid artery atheroma

A. Mupparapu M, Abomr D, Nath S. Calcified carotid artery atheroma and stroke risk assessment. Use of Doppler ultrasonography as a secondary marker: a meta-analysis. *QUINTESSENCE INTERNATIONAL*. 2021;52(4).

B. Johri AM, et al. ASECHO Assessment of Carotid Plaque by Ultrasound for the Characterization of Atherosclerosis and Evaluation of Cardiovascular Risk Guideline Summary, 2020. Guideline Central. Accessed October 16, 2023. https://www.guidelinecentral.com/guideline/302372

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Apolipoprotein A1 (APOA1)

Biomarker name: Apolipoprotein A1 (APOA1) [A]

Biomarker context: Apolipoprotein A1 (APOA1) is a key protein in high-density lipoprotein (HDL) known for its anti-inflammatory and antioxidant properties, crucial for protecting the vascular system from oxidative stress. Research indicates that APOA1 levels decrease in patients with stroke and infection. Additionally, the novel biomarker APOA1-UP, with high sensitivity (91%) and specificity (97%), has emerged as a promising independent predictor of ischemic stroke (IS).

Test definition: Blood biomarker APOA1 for early-stage screening in suspected patients of ischaemic stroke.

Results of the search

No guidelines for the test definition were identified in Guideline Central. The terms used in TRIP yielded three results. Two of them mentioned the use of APOA1 levels to determine the need for statin therapy after the patients have had a stroke and need treatment, and not for the early-stage screening of stroke [B,C]. One guideline by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) from 2011 describes the use of APOA1 level as a risk factor for cardiovascular disease [B]. In the guideline cardiovascular disease encompasses coronary artery disease, ischaemic stroke, and peripheral artery disease. Hence this guideline has been documented as relevant.

Evidence of clinical utility for the test

Evidence 1: ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) [B].

The guideline identified, details that “individuals with low HDL-C or apolipoprotein A1 (apo A1), increased TG, fibrinogen, homocysteine, apolipoprotein B (apo B), and lipoprotein(a) [Lp(a)] levels, familial hypercholesterolaemia (FH), or increased hs-CRP indicate a higher level of risk in both genders and all age groups for ischaemic stroke.”

Further the guideline defines the value of low APOA1 levels “Apo A1 is the major protein of HDL and provides a good estimate of HDL concentration. Each HDL particle may carry several apo A1 molecules. Plasma apo A1 of <120 mg/dL for men and <140 mg/dL for women approximately correspond to what is considered as low for HDL-C.” The guideline suggests that the use of apolipoprotein A and B as biomarkers in diagnostic assays to measure HDL-C is advantageous as good immunochemical assays are available and fasting conditions are not required prior to the test.

Conclusion

Through our search terms we identified a guideline which matches the test definition. This suggests that the biomarker, apolipoprotein A1 has clinical utility for early-stage screening in suspected patients of ischaemic stroke. It is worth noting that our search did not identify guidelines supporting the use of this test since 2011. Identification of more recent recommendations for this test through further research into current guidelines can strengthen the support for clinical utility of this test.

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Search terms used for this biomarker

Guideline Central search terms used: Apolipoprotein A1 (APOA1)

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: ischaemic stroke

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: Apolipoprotein A1 (APOA1)

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: prevent prevention preventive primary secondary screen screening

A. Jadav RK, Mortazavi R, Yee KC. Blood Biomarkers for Triaging Patients for Suspected Stroke: Every Minute Counts. *J Clin Med*. 2022;11(14):4243. doi:10.3390/jcm11144243

B. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J*. 2011;32(14):1769-1818. doi:10.1093/eurheartj/ehr158

C. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188. doi:10.1093/eurheartj/ehz455

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Cohorts for Heart and Aging Research in Genomic Epidemiology model for AF (CHARGE-AF) prediction model

Biomarker name: Cohorts for Heart and Aging Research in Genomic Epidemiology model for AF (CHARGE-AF) prediction model [A]

Biomarker context: One of the most common forms of arrhythmias in clinical practice is atrial fibrillation (AF). By pooling data of diverse populations from large cohorts ((Atherosclerosis Risk in Communities study, Cardiovascular Health Study and Framingham Heart Study) the Cohorts for Heart and Aging Research in Genomic Epidemiology model for AF (CHARGE-AF) prediction model was developed. It is a 5-year predictive model that accounts for variables that determine risk of AF such as age, race, height, weight, systolic and diastolic blood pressure, current smoking, use of antihypertensive medication, diabetes mellitus, history of myocardial infarction and heart failure.

Test definitions:

1. CHARGE-AF Prediction Model for primary screening of atrial fibrillation in adults
2. CHARGE-AF Prediction Model for primary screening of atrial fibrillation in European populations
3. CHARGE-AF Prediction Model for primary screening of atrial fibrillation in patients above the age of 65 years

Results of the search

No results were identified in Guideline Central. The search terms yielded four results in the TRIP PICO search out of which two guidelines mentioned the use of the model. The guideline by the European Heart Rhythm Association (EHRA) [B] was relevant and has been documented as evidence. Additionally, a scientific statement document by the American Heart Association[3] assessed the benefit of using polygenic risk scores with the CHARGE-AF model to improve accuracy. This may be relevant for future searches looking at PRS and hence has been recorded as well.

Evidence of clinical utility for the test

Evidence for test definition 1 and 3

Evidence 1: Screening for atrial fibrillation: a European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulacion Cardıaca y Electrofisiologıa (SOLAECE)" [B]

The guideline, " with a TRIP score of 7, states that "The Cohort for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium developed and validated a further risk score using data from five European and US cohorts. In the CHARGE study, a model incorporating age, race, height, weight, systolic and diastolic blood pressure, current smoking, use of antihypertensive drugs, diabetes, and history of myocardial infarction and heart failure was found to have reasonable discrimination (C statistic 0.77, 95% CI 0.75–0.78) in prediction of AF over 5 years."

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Evidence 2: Polygenic Risk Scores for Cardiovascular Disease: A Scientific Statement From the American Heart Association [C]

This evidence, which has a TRIP score of 8, states that "For adult patients, established AF risk prediction tools (CHARGE-AF) are improved with the addition of PRSs (across sexes and age groups [18–85 years]). Furthermore, given the lack of clinical risk factors, only PRSs can predict the development of early-onset AF. Future studies should focus on AF surveillance and risk mitigation strategies for high AF PRSs, as well as cost-effectiveness. The decreasing costs of genetic testing and the ability to calculate PRSs for a large number of diseases from one test increase the likelihood of cost-effectiveness, but this is yet to be formally studied for AF."

Conclusion

From our search there is sufficient evidence for clinical utility of CHARGE-AF Prediction Model for primary screening of atrial fibrillation in adult patients between the ages of 18 and 85 years. Furthermore, there is evidence to show that research has been carried out to improve accuracy of the tool by incorporating polygenic risk scores. Since the model has been developed using data from large European studies, it is suggested that the model may be more effective in patients of European ancestry [A]. However, the evidence identified did not mention the use of the model specifically in European populations and hence, further research is needed to confirm the clinical utility of the model in European populations.

Search terms used for this biomarker

Guideline Central search terms used: Cohorts for Heart and Aging Research in Genomic Epidemiology model for AF (CHARGE-AF) prediction model; CHARGE-AF

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: Atrial fibrillation

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: Cohorts for Heart and Aging Research in Genomic Epidemiology model for AF (CHARGE-AF) prediction model; CHARGE-AF; prediction models

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: general; European; older (>65yrs)

A. Himmelreich JCL, Veelers L, Lucassen WAM, et al. Prediction models for atrial fibrillation applicable in the community: a systematic review and meta-analysis. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol*. 2020;22(5):684-694. doi:10.1093/europace/euaa005

B. Mairesse GH, Moran P, Van Gelder IC, et al. Screening for atrial fibrillation: a European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE). *EP Eur*. 2017;19(10):1589-1623. doi:10.1093/europace/eux177

C. O'Sullivan JW. Polygenic Risk Scores for Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2022;146(8):e93-e118. doi:https://doi.org/10.1161/CIR.0000000000001077

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The Risk Equations for Complications of Type 2 Diabetes (RECODe) score

Biomarker name: The Risk Equations for Complications of Type 2 Diabetes (RECODe) score [A]

Biomarker context: The RECODe score comprises multiple risk equations, the sum of which can be used to guide clinical decisions and population health management. The score has been validated for predicting microvascular and macrovascular outcomes in Type Two Diabetes Mellitus (T2DM) later in life.

Test definition 1: RECODe can be used to identify T2DM patients at risk of MI later in life.

Test definition 2: RECODe can be used to identify T2DM patients at risk of stroke later in life.

Results of the search: Searching for RECODe associated with MI or stroke returned no results in Guideline Central. Within TRIP the search terms identified one guideline that recommended the use of RECODe in a T2DM clinical care pathway.

Evidence of clinical utility for the test

Evidence 1: SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline [B].

The document was published in 2021 as part of the *BMJ* Rapid Recommendations series. The purpose of these documents is to provide clinicians with trustworthy recommendations for potentially practice changing evidence. The series represents a collaborative project between the MAGIC group (https://magicevidence.org) and *The BMJ.* The document was produced by a panel of international patients, clinicians and methodologists using the GRADE approach.

The document identified is a guideline advising clinicians which T2DM patient groups could benefit from the use of SGLT-2 inhibitors or GLP-1 receptor agonists. Rather than continuing to make decisions about T2DM treatment based on glycaemic control the guideline panel issued a set of risk-stratified guidelines concerning the use of these treatments in T2DM. Following a review of evidence, the panel determined that the absolute benefits of SGLT-2 inhibitors and GLP-1 receptor agonists depend on the patients baseline risk of cardiovascular disease, which includes the risk of MI and stroke. RECODe was identified as the most credible risk prediction model for this purpose and the document recommends that clinicians use it to risk-stratify their T2DM patients prior to treatment with GLT-2 inhibitors or GLP-1 receptor agonists.

Conclusion

We have found evidence for the clinical utility of the RECODe score in predicting MI or stroke in T2DM patients. In this case use of the score then directly impacted the treatment plan for T2DM patients with the goal of maximising the benefits of using SGLT-2 inhibitors or GLP-1 receptor agonists in specific patients to reduce the incidence of future CVD events.

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Search terms used for this biomarker

Guideline Central search terms used: RECODe

Additional search parameters (or filters) used: Risk Equations for Complications of Type 2 Diabetes

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: myocardial infarction

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: RECODe

A. Buchan TA, Malik A, Chan C, et al. Predictive models for cardiovascular and kidney outcomes in patients with type 2 diabetes: systematic review and meta-analyses. *Heart*. 2021;107(24):1962-1973. doi:10.1136/heartjnl-2021-319243

B. Li S, Vandvik PO, Lytvyn L, et al. SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline. *BMJ*. Published online May 11, 2021:n1091. doi:10.1136/bmj.n1091

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3.2.3 Tests with no evidence – CVD

Most of our searches did not identify either positive or negative evidence of clinical utility of the test (Table 3.2C). This result was not unexpected, since the aim of Task 2.1.2 was to identify novel biomarkers, which will be in the early research and development stage rather than at the point of implementation for clinical use.

Integrating genomic testing and results into healthcare systems is part of the current strategy to bring genomic medicine to the forefront in many countries However, none of the tests with genetic biomarkers had any evidence regarding their clinical utility. As with the non-genetic tests this result was not unexpected considering our search was for novel biomarkers. In some cases, search results returned documents that did not fit the test definition but referenced the biomarker. These instances primarily concerned meta-analyses and primary research demonstrating research activity in the biomarker of interest.

TABLE 3.2C. Tests with no evidence of clinical utility, CVD. Reports available from the authors on request.

Test	Biomarker
Genetic test for the *ABCA1* gene to predict the risk of **ischemic stroke** in a Chinese population.	Adenosine triphosphate (ATP) binding cassette subfamily A member 1 (*ABCA1*) gene.
Genetic test for the *ACE* gene to: 1. Predict risk of **haemorrhagic stroke** in a general population OR 2. Predict risk for **haemorrhagic stroke** in Asian populations.	Angiotensin Converting Enzyme (*ACE*) gene
BAC measurement during routine mammography to identify women in the general population at increased risk of **coronary artery disease (CAD).**	Breast arterial calcification (BAC)
CHARGE-AF Prediction Model for primary screening of **atrial fibrillation** in European populations	Heart and Aging Research in Genomic Epidemiology model for AF (CHARGE-AF) prediction model
Circulating CRP enzyme-linked immunosorbent assay (ELISA) to provide non-invasive diagnosis of **abdominal aortic aneurysm (AAA)** in 1. European populations OR 2. Oceanian populations	C-reactive protein (CRP)
A genetic test to identify polymorphisms in the CRP gene which are associated with increased risk of **abdominal aortic aneurysm (AAA)** in 1. European populations OR 2. Oceanian populations.	C-reactive protein (CRP) gene
ECG algorithm measuring atrial activity to detect:	Surface electrocardiography (ECG) algorithms measuring atrial activity

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1. **Atrial fibrillation (AF)** OR 2. **AF** in patients with cardiovascular disease.	
ECG algorithm measuring ventricular activity to detect **AF** in patients with: 1. cardiac arrhythmia OR 2. cardiac arrhythmia with additional CVD.	Surface ECG algorithms measuring ventricular activity
Glycogen phosphorylase BB blood test to predict the risk of **myocardial infarction (MI**) in the general population.	Glycogen phosphorylase BB (GBPP)
Genetic test for the *GPX4* gene to determine the risk of: 1. **ischemic stroke** in a general population. 2. **hypertension** in a general population.	Glutathione peroxidase 4 (*GPX4*) gene
Genetic test for the *GSTP1* gene to predict the risk of **coronary artery disease (CAD).**	Glutathione-S-Transferase (GST)- *GSTP1* variant
Genetic test to identify the *GSTM1-GSTT1* null genotype to predict the risk of **coronary artery disease (CAD)**.	Glutathione-S-Transferase (GST)- *GSTM1-GSTT1* null genotype
A genetic test to identify the *GSTM1* null genotype to predict the risk of **coronary artery disease (CAD)** in: 1. A general population 2. An Asian population 3. People with smoking history.	Glutathione-S-Transferase (GST)- *GSTM1* null genotype
H-FABP blood test for early-stage screening of suspected patients 1. with **ischaemic stroke** OR 2. **haemorrhagic stroke**	Heart type fatty acid binding protein (H-FABP)
Circulating IL-6 blood test to assess risk of **abdominal aortic aneurysm (AAA).**	Interleukin 6 (IL-6)
Genetic test for the *IL-10* gene to predict the risk of developing **abdominal aortic aneurysm (AAA)** in a general population.	Interleukin-10 (*IL-10*) gene
Measurement of LASr by echocardiography to predict risk of: 1. **atrial fibrillation (AF)** OR 2. **stroke** in patients with chronic kidney disease (CKD)	Left atrial strain (LASr)
rt-qPCR measurement of the ratio of average telomere length to identify individuals in the general population who may have stable or unstable **coronary artery disease (CAD).**	Leukocyte telomere length

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Genetic test for the *MIF* gene to predict the risk of **coronary artery disease (CAD)** in: 1. people of Caucasian descent 2. people of Asian descent.	Macrophage migration inhibitory factor (*MIF*) gene
A blood test to determine *MMP-9* serum concentration for early-stage screening of: 1. **ischaemic stroke** OR 2. **haemorrhagic stroke**	Matrix metalloproteinase-9 (*MMP-9*); gelatinase B
A genetic test for the *MMP-9* gene for early detection of 1. **coronary artery disease (CAD)** in a general population 2. **CAD** in Asian populations. 3. **ischemic stroke (IS)** in a general population 4. in patients with **large artery atherosclerosis** 5. in patients above the age of 65yrs 6. in diabetic patients 7. in a smoking population.	Matrix Metalloproteinase-9 (MMP-9) gene
A genetic test for the *MTHFR* gene to establish the risk of **ischemic stroke** in Asian populations.	Methylenetetrahydrofolate reductase (*MTHFR*) gene
NDKA blood test for early detection of: 1. **transient ischaemic attack** OR 2. **haemorrhagic stroke** OR 3. **ischaemic stroke**	Nucleoside diphosphate kinase A (NDKA)
The measurement of NR2 peptide concentrations, using a commercial absorbance test, to diagnose **stroke** by rapidly differentiating between acute ischemic stroke and stroke mimics.	NR2 peptide (aka N-methyl-D-aspartate, NMDA)
Genetic test for the *NF-kB1* gene to predict the risk of **coronary artery disease (CAD).**	Nuclear factor kappa B subunit 1 (*NF-kB1*) gene
Panoramic radiography to detect atheroma or atherosclerosis and identify people at increased risk of **cardiovascular disease (CVD).**	Carotid atherosclerosis; calcified carotid artery atheroma
Assessment of retinal vascular calibre during retinal photography to identify: 1. women at an increased risk of **coronary artery disease (CAD)** OR 2. improve risk stratification of patients at risk of **stroke.**	Retinal vascular calibre
Assessment of retinal vascular calibre using flicker light-induced dilatation of retinal	Retinal vascular calibre

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arterioles (FIDart) to predict the risk of **coronary artery disease (CAD)** in the general population	
The SMARTChip biosensor to detect purines in whole blood for the diagnosis of **ischemic stroke** by differentiating between a genuine stroke and a stroke mimic in a general population.	Blood purines detected by a point-of-care biosensor SMARTChip
Use of the 'suiteHEART' software, as a user independent automated volumetric analysis tool of cardiovascular magnetic resonance imaging (MRI) in an ischemic heart disease population to assess risk of additional **cardiovascular disease (CVD)** events.	Automated volumetric analysis of cardiovascular magnetic resonance imaging using artificial intelligence (AI)

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3.2.4 Genetic tests search results – CVD

Genetic testing for CVD can offer valuable insights into an individual's risk, prognosis, and potential treatment strategies. Progress in human genetics is enhancing our understanding of various inherited cardiovascular conditions, for example cardiomyopathies, arrhythmic disorders, vascular malformations, and lipid disorders such as familial hypercholesterolemia. The information derived from genetic testing can be useful in the clinical management of these conditions. Hence, there is a growing interest in the clinical use of genetic testing to identify individuals at risk of CVD at an early stage.

To assess the impact the research in this field has on clinical management and to identify any guidelines that may already be in use, we conducted searches in the same databases using terms for genetic tests and cardiovascular disease. We identified ten guidelines that recommend the use of genetic testing in the clinic. These were all guidelines related to cardiomyopathies and they recommend the use of genetic testing and genetic counselling for high-risk individuals with a strong family history of the disease. We also identified one guideline that does not support the use of genetic testing for individuals at risk of atrial fibrillation.

Test definition: Genetic tests for early detection, risk prediction and the potential prevention of cardiovascular disease

Search strategy:

For the purposes of this search, genetic testing did not include polygenic scores, which were searched for separately.

Evidence for clinical utility

Evidence supporting the use of genetic testing in clinic

Evidence 1: Korean Society of Heart Failure Guidelines for the Management of Heart Failure: Definition and Diagnosis [A] TRIP SCORE: not assessed

- Guidelines by the Korean Society for Heart Failure, 2023
- Genetic testing for familial cardiomyopathy is recommended for clinical use.

“Identifying the etiology of HF is essential for its treatment and prognosis prediction. The diverse causes of HF can be assessed through various imaging, blood, and genetic tests.”

“Patients with suspected hereditary or familial cardiomyopathy should be advised genetic testing for identifying the cause of the disease. (Class I, Level of Evidence B)”

“All immediate family members (parents, siblings, and children) of patients with cardiomyopathy with a clear genetic mutation should undergo genetic testing. (Class I, Level of Evidence B according to the New York Heart Association functional classification*.)

** Class I refers to no symptoms with normal physical activity. Level of evidence/ stage of heart failure B refers to people without current or previous symptoms of heart failure but with either structural heart disease, increased filling pressures in the heart or other risk*

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factors. https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure

Evidence 2: 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC) [B] TRIP SCORE: 3

- Guideline by the European Society for Cardiology, 2022
- Genetic testing for hypertrophic cardiomyopathy is recommended for clinical use.

"HCM is characterized by increased LV wall thickness not explained by abnormal loading conditions (such as hypertension or valvular disease). Because the natural history and management differs according to the underlying aetiology of LVH, diagnostic work-up is of paramount importance and includes CMR and genetic testing. HCM is usually caused by a mutation with autosomal dominant inheritance, supporting cardiac screening in first-degree relatives, in parallel with genetic testing in the index patient."

"Patients with genetic cardiomyopathies and arrhythmia syndromes require genetic testing as a routine part of their care."

Evidence 3: Genetic Testing for Hereditary Cardiac Disease: Clinical Appropriateness Guidelines [C] TRIP SCORE: 0

- Guidelines developed by, and used with permission from, Informed Medical Decisions, 2022
- Genetic testing for hypertrophic cardiomyopathy is recommended for clinical use.

"In addition to appropriate use criteria, confirmatory or diagnostic genetic testing for hereditary arrhythmias (i.e., Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Long QT syndrome (LQTS)) and cardiomyopathies (i.e., arrhythmogenic right ventricular cardiomyopathy (ARVC), dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), left ventricular non-compaction cardiomyopathy (LVNC), restrictive cardiomyopathy (RCM)) is medically necessary when all of the following criteria are met:

- The individual has a clinical diagnosis of a hereditary cardiomyopathy or arrhythmia OR the individual has a suspected syndromic, metabolic or neuromuscular form of a hereditary cardiomyopathy or arrhythmia
- The requested testing is as targeted as possible to a specific subset of genes with a demonstrated gene/disease association with the individual's diagnosed or suspected condition"

"Single-site genetic testing of asymptomatic individuals for a known familial deleterious or suspected deleterious pathogenic or likely pathogenic (P/LP) variant is medically necessary."

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Evidence 4: 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC)[D] TRIP SCORE: 3

- Guidelines by the European Society of Cardiology, 2021
- Genetic testing for cardiomyopathy is recommended for clinical use.

"Patients who could have genetic dyslipidaemias, such as heterozygous FH, can be identified by extreme lipid abnormalities and/or family history. An LDL-C >4.9 mmol/L (190 mg/dL) in therapy-naïve patients requires careful evaluation for possible FH. However, in the presence of premature ASCVD or family history, possible FH should be considered at lower LDL-C levels. Besides genetic testing (not always affordable), use of the Dutch Clinical Lipid Network criteria is recommended to identify possible FH. Homozygous FH is rare and should always be placed under the care of lipid experts."

Evidence 5: 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [E] TRIP SCORE: 8

- Guideline by the American Heart Association and American College of Cardiology, 2020
- Genetic testing for hypertrophic cardiomyopathy is recommended for clinical use.

"Counselling patients with HCM regarding the potential for genetic transmission of HCM is one of the cornerstones of care. Screening first-degree family members of patients with HCM, using either genetic testing or an imaging/electrocardiographic surveillance protocol, can begin at any age and can be influenced by specifics of the patient/family history and family preference. As screening recommendations for family members hinge on the pathogenicity of any detected variants, the reported pathogenicity should be reconfirmed every 2 to 3 years."

"In patients with HCM, genetic testing is beneficial to elucidate the genetic basis to facilitate the identification of family members at risk for developing HCM (cascade testing)"

"When performing genetic testing in an HCM proband, the initial tier of genes tested should include genes with strong evidence to be disease-causing in HCM"

"In patients with HCM who harbor a variant of uncertain significance, the usefulness of clinical genetic testing of phenotype-negative relatives for the purpose of variant reclassification is uncertain."

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"For patients with HCM who have undergone genetic testing and were found to have no pathogenic variants (i.e., harbor only benign/likely benign variants), cascade genetic testing of the family is not useful."

"Genetic testing in HCM has several clinical benefits, including confirmation of the diagnosis, preclinical diagnosis, cascade genetic testing in the family, and in guiding reproductive decisions. Cascade genetic testing in the family identifies those who carry the disease-causing variant and require ongoing surveillance, while those who do not carry the variant can be released from lifelong clinical surveillance."

"Genes associated with HCM phenocopies may be included in first-tier genetic testing if there is clinical suspicion based on phenotype evaluation of a systemic disorder, including PRKAG2 (glycogen storage disease), LAMP2 (Danon disease), GLA (Fabry disease), transthyretin amyloid cardiomyopathy, and disease genes related to RASopathies. In some circumstances, the genetic test result may alter the management of the index case, such as enzyme replacement therapy in patients with Fabry disease or more aggressive clinical management of patients with Danon disease."

Evidence 6: Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement From the American Heart Association [F] TRIP SCORE: 8

- Guideline by the American Heart Association, 2020
- Genetic testing is recommended for inherited cardiovascular conditions such as cardiomyopathies and arrhythmias.

"Genetic testing is informative and useful for the clinical management of various inherited cardiovascular diseases such as cardiomyopathies, arrhythmic disorders, thoracic aortic aneurysms and dissections, and familial hypercholesterolemia (FH)."

"Genetic testing typically should be reserved for patients with a confirmed or suspected diagnosis of an inherited cardiovascular disease or for individuals at high a priori risk resulting from a previously identified pathogenic variant in their family (although similar in meaning, we use the term variant in preference to mutation in this statement). One crucial element is rigorous, disease-appropriate phenotyping, either by the provider or via referral to a specialist. The second element, which cannot be overemphasized, is a comprehensive family history that spans at least 3 generations. If these 2 elements together establish or strongly suggest an inherited cardiovascular disease, then the next step is to identify the most appropriate person for genetic testing. For reasons of practicality, the provider often will need to test the patient presenting to the clinic first, but in principle, the family member with the most definitive and most severe phenotype should be the one initially tested to increase the chances of identifying pathogenic variant(s) useful for familial testing."

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"A family history of at least 3 generations should be obtained for all patients with a primary cardiomyopathy. Second, clinical screening for cardiomyopathy is recommended for at-risk first-degree relatives. Third, patients with genetic, familial, or other unexplained forms of cardiomyopathy should be referred to expert centers. Genetic counselling is recommended for all patients with cardiomyopathy and their family members. The authors also recommended that genetic testing be offered to all patients diagnosed with all recognized forms of cardiomyopathy."

Evidence 7: Sudden Cardiac Arrest Survivorship: A Scientific Statement From the American Heart Association [G] TRIP SCORE: 8

- Guideline by the American Heart Association, 2020
- Genetic testing may be useful to predict risk and diagnose arrhythmias and cardiomyopathies.

"Patients with inherited arrhythmia syndromes, which span both channelopathies and cardiomyopathies, may benefit from formal genetic counselling, testing, and familial evaluations. In such patients, the yield of genetic evaluation varies substantially by condition but can facilitate screening and direct carrier testing of relatives at risk for the condition. Genomic analysis with commercial genetic testing has increased dramatically as sequencing technology has become highly efficient, making test selection and variant interpretation more complex. Moreover, discussion of legal, economic, and ethical implications of testing is warranted when counselling patients. Testing in conjunction with an experienced genetic counsellor is highly encouraged."

Evidence 8: Heart Failure in the Era of Precision Medicine: A Scientific Statement From the American Heart Association [H] TRIP SCORE: 8

- Statement by the American Heart Association, 2019
- Genetic testing is recommended for patients with heart failure, diagnosed with cardiomyopathy or arrhythmia.

"If a patient with HF is diagnosed with hypertrophic cardiomyopathy (HCM), DCM, arrhythmogenic right ventricular cardiomyopathy, noncompaction cardiomyopathy, or restrictive cardiomyopathy, a comprehensive pedigree should be obtained (ideally ≥3 generations), and clinical genetic testing should be considered."

"The major utility of genetic testing currently is to provide risk stratification of family members if a pathogenic variant is identified in the proband; targeted testing for the same pathogenic variant can be considered for any first-degree blood relative."

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Evidence 9: Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG) [I] TRIP SCORE: 4

- Guideline by the American college of Medical Genetics and Genomics, 2018
- Genetic testing for cardiomyopathy is recommended for clinical use.

"A genetic evaluation of cardiomyopathy is indicated with a cardiomyopathy diagnosis, which includes genetic testing. Guidance is also provided for clinical approaches to secondary findings from cardiomyopathy genes. This is relevant as cardiomyopathy is the phenotype associated with 27% of the genes on the ACMG list for return of secondary findings."

"Genetic testing is indicated for cardiomyopathy to assist in patient care and management of at-risk family members."

Evidence 10: 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy [J] TRIP SCORE: 3

- Guideline by the European Society of Cardiology, 2014
- Genetic testing for hypertrophic cardiomyopathy is recommended for clinical use.

"The task force acknowledge that limited resources make implementation of genetic testing challenging in some healthcare systems. Nevertheless, identification of causative mutations facilitates pre symptomatic diagnosis of family members, clinical surveillance, and reproductive advice. For this reason, genetic testing is recommended in patients fulfilling diagnostic criteria for HCM to enable cascade genetic screening of their relatives."

"The lack of robust data on specific genotype–phenotype associations means that the impact of genetic testing on clinical management is limited mostly to some of the rare genetic causes of HCM. Genetic testing may be of limited clinical value when first degree relatives are unavailable or unwilling to consider screening for the disease. Genetic testing in individuals with an equivocal clinical diagnosis (e.g. athletes and hypertensives), should only be performed after detailed clinical and family assessment by teams experienced in the diagnosis and management of cardiomyopathies as the absence of a sarcomere mutation does not exclude familial HCM and variants of uncertain significance are difficult to interpret."

Evidence against the use of genetic testing in clinic

Evidence 11: 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation [K] TRIP SCORE: 8

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- Guideline by the American Heart Association and American College of Cardiology, 2014
- Genetic testing in clinic is not recommended for Atrial Fibrillation (AF)

"AF is heritable, and having an affected family member is associated with a 40% increased risk of the arrhythmia. Premature AF, defined as a first-degree relative with onset of AF before the age of 66, is associated with a doubling in risk of AF. Thus, it is common, particularly among younger, healthier persons with AF, to observe families with AF. In the last 10 years, many mutations have been identified in individuals and families with AF. The implicated genes include a wide range of ion channels, signalling molecules, and related proteins; however, the role of these mutations in more common forms of AF appears limited. Population-based or genome wide association studies identified 9 distinct genetic loci for AF. Furthermore, combinations of AF-associated single nucleotide polymorphisms may identify individuals at high risk for arrhythmia. However, the role of these common genetic variants in risk stratification, assessment of disease progression, and determination of clinical outcomes is limited. **Routine genetic testing related to AF is not indicated."**

Conclusion of the genetic test search

Guidelines recommending genetic testing for conditions such as cardiomyopathies and arrhythmias, that have a strong genetic basis, are well established. Genetic testing is generally recommended for patients already diagnosed with or suspected of having an inherited CVD, or for those with a high risk due to a previously identified pathogenic variant. An essential factor in the recommended guidelines is thorough and disease-specific phenotyping, conducted either by the healthcare provider or through referral to a specialist. Equally crucial is a comprehensive family history spanning at least three generations. The guidelines further detail targeted diagnostic testing and genetic counselling pathways for patients with strong familial history of CVD, Type 2 diabetes, high cholesterol, and high blood pressure.

However, for other CVD such as atrial fibrillation and stroke, routine genetic testing is currently not recommended. Strokes and atrial fibrillation are complex conditions influenced by a combination of genetic, environmental, and lifestyle factors. Common risk factors for stroke and atrial fibrillation such as hypertension and diabetes are well-established. These factors are more easily identifiable and able to be managed through routine clinical assessments and lifestyle interventions. Due to a lack of evidence on the role of genetic variants on risk prediction, disease progression and clinical outcomes of stroke and atrial fibrillation, current guidelines do not recommend genetic testing for these conditions.

Hence, from our search, we have identified guidelines which recommend genetic testing as useful in predicting risk for certain CVD with a strong genetic bases such as cardiomyopathies, but at present do not recommend testing for other conditions such as stroke and atrial fibrillation due to a lack of evidence.

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Search terms used for this biomarker

Guideline Central search terms used: genetic test AND cardiovascular

Additional parameters: cardiology

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: cardiovascular disease

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: genetic test

A. Cho JY, Cho DH, Youn JC, et al. Korean Society of Heart Failure Guidelines for the Management of Heart Failure: Definition and Diagnosis. Korean Circ J. 2023;53(4):195-216. doi:10.4070/kcj.2023.0046
B. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2022;43(40):3997-4126. doi:10.1093/eurheartj/ehac262
C. No author. Clinical Appropriateness Guidelines: Genetic Testing for Hereditary Cardiac Disease, Aim speciality health 2022, https://providers.carelonmedicalbenefitsmanagement.com/genetictesting/wp-content/uploads/sites/15/2022/03/GT05-Hereditary-Cardiac-v2.2022-FINAL-PDF.pdf
D. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). Eur Heart J. 2021;42(34):3227-3337. doi:10.1093/eurheartj/ehab484
E. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2020;76(25):e159-e240. doi:10.1016/j.jacc.2020.08.045
F. Musunuru K, Hershberger RE, Day SM, et al. Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement From the American Heart Association. Circ Genomic Precis Med. 2020;13(4):e000067. doi:10.1161/HCG.0000000000000067
G. Sawyer KN, Camp-Rogers TR, Kotini-Shah P, et al. Sudden Cardiac Arrest Survivorship: A Scientific Statement From the American Heart Association. Circulation. 2020;141(12). doi:10.1161/CIR.0000000000000747
H. Cresci S, Pereira NL, Ahmad F, et al. Heart Failure in the Era of Precision Medicine: A Scientific Statement From the American Heart Association. Circ Genomic Precis Med. 2019;12(10):e000058. doi:10.1161/HCG.0000000000000058
I. Hershberger RE, Givertz MM, Ho CY, et al. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018;20(9):899-909. doi:10.1038/s41436-018-0039-z

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J. Authors/Task Force members, Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733-2779. doi:10.1093/eurheartj/ehu284

K. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. J Am Coll Cardiol. 2014;64(21):e1-e76. doi:10.1016/j.jacc.2014.03.022

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3.2.5 PRS search results – CVD

Cardiovascular disease (CVD) is a leading cause of premature death and disability. Current risk prediction efforts have limitations, prompting a shift towards genetic characterisation for earlier and personalised prevention. While rare genetic variants contribute to familial risk, studies suggest a broader heritability in the general population. Advances in genetic profiling, especially since the Human Genome Project, have enabled cost-effective population-based studies. Genome-wide association studies reveal causal mechanisms, and systematic cataloguing of risk alleles has led to the development of polygenic risk scores (PRS), enhancing cardiovascular risk prediction.

To identify evidence for utility of PRS for CVD we carried out a search using terms targeting CVD as a whole and then diving deeper into individual diseases under the category of CVD. Individual diseases searched include stroke, ischemic heart disease (IHD)- myocardial infarction (MI) and coronary artery disease (CAD), abdominal aortic aneurysm (AAA), atrial fibrillation (AF), hypertension, risk of CVD and atherosclerotic cardiovascular disease, peripheral arterial disease (PAD), cardiomyopathy and myocarditis, major adverse cardiac events (MACE), non-rheumatic valvular heart disease.

Overall, we identified six guidelines including PRS for cardiovascular disease. Disease specific searches resulted in the same guidelines being identified. Of the six guidelines only one was for a specific CVD, namely AF and one looked at complex chronic diseases, with CVD being one disease discussed. The remaining guidelines were for CVD in general and would then mention or disease a variety of different CVDs such as AF, stroke, CAD, AAA, MI, or PAD. Atherosclerotic CVD was also considered.

Biomarker context: PRS for CVD are sophisticated tools that leverage insights from genetics to assess an individual's susceptibility to developing cardiovascular conditions. The rationale behind PRS lies in the complex nature of CVD, where multiple genetic factors contribute to overall risk.

Test definition: Polygenic risk scores for early detection and risk prediction for the potential prevention of cardiovascular disease

Evidence of clinical utility for the test

Below is a summary of the findings obtained from the search conducted using the terms "polygenic" and "cardiovascular disease." The results listed from newest to oldest, were also found in searches using terms specific to the diseases under investigation. Quotes from the guidelines that discuss polygenic scores are included below.

Evidence 1: ACMG STATEMENT: The clinical application of polygenic risk scores: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG) [A]
TRIP SCORE: 4

- Report by the American College of Medical Genetics and Genomics, 2023
- At present, the ACMG advocates against clinical implementation of PRS testing unless the provider and patient have a clear understanding of the

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limitations of the testing and applicability to the specific patient, including how the results will be used to guide evidence based clinical care. .

"The ACMG has developed this Points to Consider document to address the potential value of PRS given the limited evidence-base for clinical utility."

"Appropriate genetic counseling and informed consent is crucial before PRS testing. It is important to highlight critical differences between testing for monogenic disorders and PRS testing. For example, the clinical utility including accuracy of PRS in various clinical conditions is not very well established."

"As PRS tests are being developed for implementation in the clinical settings, it is important to continue to monitor progress and to focus on key considerations including main advantages and limitations of PRS testing, such as its clinical utility, the inclusion of multiple ethnicities, and the advances in technology as new evidence is generated."

"Key learning points: At this time, the ACMG advocates against clinical implementation of PRS testing unless the provider and patient have a clear understanding of the limitations of the testing and applicability to the specific patient, including how the results will be used to guide evidence based clinical care."

Evidence 2: Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [B] (No TRIP score as only found in Guideline central database)

- Report by The American Heart Association, American College of Cardiology, and the Heart Rhythm Society, 2023
- Polygenic risk scores are not recommended for AF at present.

Future research needs number 16: "Genetic testing: The use and applicability of consumer-based or targeted genetic testing for AF remains uncertain. Polygenic risk scores can indicate higher risk for AF, but the use of genetic testing to impact clinical surveillance, management, and clinical outcomes remains uncertain."

Evidence 3: Polygenic Risk Scores for Cardiovascular Disease: A Scientific Statement from the American Heart Association [C] TRIP SCORE: 8

- Report by The American Heart Association, 2022
- CVDs considered in this report include AF, stroke, CAD, AAA, MI, and PAD.

Evidence suggests that PRS may be useful in prediction risk of conditions such as atrial fibrillation, CAD, and MI. Additionally, PRS for predicting high levels of LDL-C which is known to have a link with conditions such as stroke, PAD and AAA, may be useful in predicting risk of these condition. However, at present there is insufficient evidence to recommend the use of PRS in clinic for CVD.

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General comment: Atherosclerosis, Hypercholesterolemia or high blood cholesterol levels are known to put patients at increased risk of developing CVD such as CAD or ASCVD. Hence, guidelines related to polygenic scores for other conditions such as hypercholesterolemia that put people at an increased risk of CVD are also considered in the guidelines.

CVDs considered in this report include AF, stroke, CAD, AAA, MI, and PAD.

Evidence 4: 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC) [D] TRIP SCORE: 3

- Guideline by the European Society for Cardiology, 2021
- ASCVD risk factors and comorbidities affect lifetime risk of AF. Control of ASCVD Risk factors may reduce risk of AF.

"ASCVD risk factor burden and comorbidities, including lifestyle factors, and age significantly affect the lifetime risk for AF development. The observed effect of clinical ASCVD risk factor burden and multiple comorbidities on the lifetime risk of AF (significantly increasing from 23.4% among individuals with an optimal clinical risk factor profile to 33.4% and 38.4% in those with borderline and elevated clinical risk factors, respectively) suggests that early intervention and control of modifiable ASCVD risk factors could reduce incident AF." "The aetiology of ASCVD has a genetic component, but this information is not currently used in preventive approaches. Advances on polygenic risk scores for risk stratification could increase the use of genetics in prevention. For ASCVD, there is, however, a lack of consensus regarding which genes and corresponding single nucleotide polymorphisms should be included, and whether to use risk factor-specific or outcome-specific polygenic risk scores. Polygenic risk scoring has shown some potential to improve ASCVD risk prediction for primary prevention, but the incremental prediction accuracy is relatively modest and needs further evaluation in both men and women. Additional evidence is also needed to evaluate the clinical utility of polygenic risk scores in other clinical settings, such as in patients with pre-existing ASCVD."

Evidence 5: Considerations for Cardiovascular Genetic and Genomic Research with Marginalized Racial and Ethnic Groups and Indigenous Peoples [E] TRIP SCORE: 8

- A scientific statement by the American Heart Association, 2021

"…., genomic research, or the study of the genome including gene-gene and gene-environment interactions, has expanded our understanding of polygenic and environmental influences in complex cardiovascular conditions. Great strides in cardiovascular genetic and genomic research have led to increased use of genetic screening, the application of

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polygenic risk scores in practice, and the use of genomic information to guide interventions. Although these advances hold tremendous potential to improve cardiovascular health and to prevent and treat cardiovascular disease, there are grave concerns that barriers to participation in genetic and genomic research will increase existing health inequities for marginalized racial and ethnic groups and Indigenous populations."

"For underrepresented populations, polygenic risk scores derived from these studies are less accurate in predicting disease phenotypes, novel population-specific genetic variations may be misclassified as potentially pathogenic, and there is a lack of understanding of how different populations metabolize drugs."

Evidence 6: Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement from the American Heart Association [F] TRIP SCORE:8

- Report by the American Heart Association, 2020
- PRS for CAD and AF are not recommended at present.

"Recent reports of polygenic risk scores for complex cardiovascular diseases such as coronary artery disease and atrial fibrillation suggest that patients with extreme scores, that is, in the top few percent of the population, have an increased risk of disease several-fold higher than that of the population average that is equivalent to risk conferred by some monogenic disorders. Whether such information is actionable and can meaningfully inform patient management remains to be determined, but with genotyping and sequencing technologies that permit the calculation of polygenic risk scores now being inexpensive enough to be incorporated into routine clinical practice, this new frontier in genetic testing will be fertile ground for investigation in the coming years."

Conclusion

From our investigation, we have found guidelines suggesting that polygenic risk scores (PRS) may hold potential in predicting cardiovascular disease (CVD) risk. However, these guidelines emphasise the need for additional evidence to fully support their use for prevention.

Recognising the crucial role of genome-wide association studies (GWAS) in identifying genetic variants linked to heightened cardiovascular risk, the guidelines acknowledge the creation of a PRS as a numerical representation of an individual's genetic predisposition to CVD. The objective of integrating PRS into cardiovascular medicine is to enhance the precision of risk prediction and stratification. When available healthcare professionals could use these scores to identify individuals with elevated risk and tailor preventive strategies, interventions, and monitoring plans accordingly. This personalised approach could facilitate early interventions, lifestyle modifications, and targeted medical treatments for those at a higher risk of developing cardiovascular issues.

Whilst the guidelines acknowledge the potential of PRS for CVD in improving risk assessment, guiding therapeutic decisions, and enhancing patient outcomes through a

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proactive and individualised approach, they stress the current lack of sufficient research and evidence. Consequently, the guidelines explicitly state that, at present, PGS for CVD are not recommended for routine use in clinical practice. However, the guidelines suggest specific use cases for PRS, such as its potential complementary role alongside other risk scoring models like CHARGE-AF to improve the accuracy of risk prediction.

The guidelines and statements underscore the importance of further research in this area before widespread implementation. Overall, the guidelines advocate for caution and a measured approach, emphasising the need for additional evidence before considering the clinical utility of polygenic risk scores in early detection and risk prediction for preventing cardiovascular diseases.

Search terms used for this biomarker

Guideline Central search terms used: polygenic score AND cardiovascular/ specific disease

Additional parameters: cardiology

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: cardiovascular

TRIP Advanced "ANY of these words" OR TRIP PICO Intervention: prevent prevention preventive primary secondary screen screening

TRIP Advanced "THIS exact phrase" OR TRIP PICO Population: polygenic score

A. Abu-El-Haija A, Reddi HV, Wand H, et al. The clinical application of polygenic risk scores: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023;25(5):100803. doi:10.1016/j.gim.2023.100803
B. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation. J Am Coll Cardiol. 2024;83(1):109-279. doi:10.1016/j.jacc.2023.08.017
C. O'Sullivan JW. Polygenic Risk Scores for Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2022;146(8):e93-e118. doi:10.1161/CIR.0000000000001077
D. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). Eur Heart J. 2021;42(34):3227-3337. doi:10.1093/eurheartj/ehab484
E. Mudd-Martin G, Cirino AL, Barcelona V, et al. Considerations for Cardiovascular Genetic and Genomic Research With Marginalized Racial and Ethnic Groups and Indigenous Peoples: A Scientific Statement From the American Heart Association. Circ Genomic Precis Med. 2021;14(4):e000084. doi:10.1161/HCG.0000000000000084

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F. Musunuru K, Hershberger RE, Day SM, et al. Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement From the American Heart Association. Circ Genomic Precis Med. 2020;13(4):e000067. doi:10.1161/HCG.0000000000000067

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3.2.6 CVD discussion

Primary prevention versus secondary prevention

Overall, the tests identified covered both primary and secondary prevention, with most tests without evidence of clinical utility pertaining to secondary prevention. This encompassed most of the blood-based biomarkers whose use was being examined for improved early detection of various CVD conditions. This included detection of by-products of cellular disturbance to improve the differentiation of ischemic stroke and stroke mimics (other medical conditions that present with symptoms similar to stroke) [30] along with detection of raised levels of interleukin-6 to improve abdominal aortic aneurysm detection [31].

In contrast, the tests with evidence supporting clinical utility frequently considered longer-term risk prediction for CVD events.

Combined test definitions for related biomarkers

In some cases, different tests involved using biomarkers in similar ways such that they can be considered together. Two main examples include tests using CAC scores and electrocardiograms (ECG).

In the case of CAC scoring, we identified evidence supporting the use of CAC scoring in determining long term risk of CVD events in a general population. We found guidelines suggesting use of CAC scoring in defined and specific use cases such as in patients 40-75 years of age, with LDL-C of 70-189mg/dL and a 10-year ASCVD risk of 5-19% to determine the need for therapies to prevent later CVD events [32]. Similarly using CAC scoring in specific areas such as a carotid atheroma was supported [33] and in diabetic populations [34]. However extrapolating CAC scoring to be used in breast tissue has not been described in guidelines, HTA or CEAs and is therefore currently not supported [35].

In the case of ECG, the definition of the test was built upon this already established technology that is used in clinical care. The tests sought to use surface ECG algorithms to improve prediction of atrial fibrillation in patients with existing cardiac issues by examining atrial activity or ventricular activity [36]. Searches for atrial or ventricular activity did not identify any evidence examining the clinical utility of this repurposed method, suggesting that outside of its well-established clinical uses these slightly altered methodologies are still in the early research stages, or these modifications are unsuitable for the proposed test.

Both the CAC scoring and ECG examples illustrate the potential of these biomarkers, particularly when the only difference in use is a change in the target population. It demonstrates that whilst these changes such as assessing different patient populations are not yet fully established and are yet to be considered for clinical practice, they are being researched and attempts are being made to improve the scope of techniques that already have established clinical use.

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Conclusion for CVD

Overall, we identified a small number of tests for CVD with evidence supporting their clinical utility. Namely, those associated with small changes to existing established techniques or those comprising multi-factorial models. Many of our searches did not identify any evidence that could be used to assess the clinical utility of our identified biomarkers and their associated tests. Again, this was not unexpected as we have been examining novel biomarkers in the early stages of development. It demonstrates that these techniques are under investigation and provide numerous potential options which may lead to improvements in primary and secondary prevention of CVD.

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3.3 Neurodegenerative diseases

In neurodegenerative diseases, as can be seen in Table 3.3A, from the 286 papers reviewed in Task 2.1.1, 17 were selected which corresponded to high quality evidence sources, including nine systematic reviews with meta-analyses and eight review papers. No RCTs were identified.

Table 3.3A. Neurodegenerative diseases papers from Task 2.1.1 prioritised for Task 2.1.2 by study type.

Total number of papers identified in the scoping review	286
Systematic review and meta-analysis papers	9
Review papers	8
RCT papers	0
Total (including genetics)	**17**

Among these papers, five were excluded due to the lack of a test definition according to our protocol.

3.3.1 Development of test definitions in neurodegenerative diseases

Twenty-six test definitions were described and there were multiple test definitions for some biomarkers, as the papers identified in Task 2.1.1 considered multiple populations or diseases of interest.

Most of the biomarkers and test definitions focused on Alzheimer's disease, which is the most frequent cause of dementia, followed by Parkinson's disease and multiple sclerosis. Only one biomarker was for vascular dementia, frontotemporal dementia and Lewy body disease, and there were no biomarkers or test definitions for amyotrophic lateral sclerosis.

After the search, evidence of clinical utility was identified for one test definition. For the remaining papers and for most of the biomarkers used and test definitions involved, no evidence was found (not corresponding to the definition of the test that was provided).

3.3.2 Tests with evidence – clinical utility not supported, neurodegenerative diseases

The single test for which we found evidence relates to an image biomarker for the prediction of the evolution from mild cognitive impairment (MCI) to Alzheimer's disease.

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TABLE 3.3B. Test with evidence not supporting their clinical utility, neurodegenerative diseases.

Test definition	Unique Biomarker Name	Page number
Cortical and hippocampal atrophy measurement using Structural magnetic resonance imaging (sMRI) in a population with Subjective cognitive decline (SCD) to predict clinical progression to mild cognitive impairment or **Alzheimer's disease**.	Cortical and hippocampal atrophy Scarth M, Rissanen I, Scholten RJPM, Geerlings MI. Chen J, ed. J Alzheimers Dis. 2021;83(3):1089-1111. doi:10.3233/JAD-210218	

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Cortical and hippocampal atrophy

Biomarker name: Cortical and hippocampal atrophy **[A]**

Biomarker context: Atrophy of the medial temporal lobe, including the hippocampus and entorhinal cortex are known to be associated with Alzheimer's disease (AD). Structural magnetic resonance imaging (sMRI) of cortical regions to measure cortical and hippocampal atrophy may be predictive of AD or progression from mild cognitive impairment (MCI) to AD.

Test definition: Cortical and hippocampal atrophy measurement using sMRI in a population with subjective cognitive decline (SCD) to predict clinical progression to MCI or AD.

Results of the search: No results were found in Guideline Central, but 12 results were found in TRIP from which one guideline (two versions) matched the test definition.

Evidence of clinical utility for the test

Evidence 1: American College of Radiology ACR Appropriateness Criteria® Dementia [B].

This guideline was published in May 2020 by the American College of Radiology and it has a TRIP score of 8. It highlights how to determine appropriate imaging examinations for differential diagnosis and treatment of specified medical conditions, in this case, dementia. For subjects with cognitive decline and suspected AD, disproportionate atrophy on structural MRI in medial, basal, and lateral temporal lobe and medial parietal cortex is one of the major AD biomarkers that is being widely researched. Medial temporal lobe atrophy has been noted to correlate with cognitive decline and nonfunctional test accumulation and is seen in patients with MCI compared with normal patients. The guidelines quotes a research study that found, among different possibilities, combination of quantitative MRI and PIB-PET was the most accurate to predict conversion from MCI to AD, but it also states that these examinations – which may be complementary to each other – are not front line for initial imaging of suspected AD.

Conclusion

Cortical and hippocampal atrophy measurement using MRI to identify cognitively normal individuals at risk of memory decline or initial Alzheimer's disease is still at the research stage.

Search terms used for this biomarker

Guideline Central search terms used: brain atrophy

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: (alzheimer AND ("brain atrophy") AND ("prevent" OR "screen" OR "early diagnos")) from_date:2013

A. Scarth M, Rissanen I, Scholten RJPM, Geerlings MI. Biomarkers of Alzheimer's Disease and Cerebrovascular Lesions and Clinical Progression in Patients with Subjective Cognitive Decline: A Systematic Review. Chen J, ed. J Alzheimers Dis. 2021;83(3):1089-1111. doi:10.3233/JAD-210218

B. Moonis G, Subramaniam RM, Trofimova A, et al. ACR Appropriateness Criteria® Dementia. J Am Coll Radiol. 2020;17(5):S100-S112. doi:10.1016/j.jacr.2020.01.040

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3.3.3 Tests with no evidence – neurodegenerative diseases

The tests in Table 3.3C include all genetic biomarkers that were identified in the results of Task 2.1.1 and prioritised for this study. Many of them had been proposed in the papers as possible tools for early detection of Alzheimer's disease or for predicting the progression to clinical disease from preclinical stages.

TABLE 3.3C. Tests for which no evidence was found regarding clinical utility, neurodegenerative diseases. Reports available from the authors on request.

Test definition	Unique Biomarker Name
16-a-hydroxypregnenolone quantification in plasma by Ultra-Performance Liquid Chromatography/Quadrupole Time-of-Flight Mass Spectrometry/Mass Spectrometry (UPLC/Q-TOF-MS/MS) for the early detection of **Alzheimer's disease (AD)** in a general population.	16-a-hydroxypregnenolone in plasma
Genetic test for the ACE gene to predict risk of **Alzheimer's disease (AD)** in a Northern European population.	Angiotensin converting enzyme (ACE) gene
Aβ42/Aβ40 ratio quantification in plasma analysed by different techniques (defined in the individual report) to predict Aβ-PET results to improve early detection of **Alzheimer's disease (AD)** in 1. A general population OR 2. Patients with mild cognitive impairment	Aβ42/Aβ40 ratio
Measurement of Aβ42 levels (via methods defined in the individual report) to predict the clinical progression of subjective cognitive decline (SCD) to **Mild cognitive impairment (MCI)** or **Alzheimer's disease (AD)** in a general population: 1. In cerebrospinal fluid (CSF) OR 2. Blood plasma.	Aβ42 levels
Genetic test for the ATP7B gene to predict risk of **Alzheimer's disease (AD)**.	ATP7B gene variant
Bone mineral density quantification in femoral neck, hip, or lumbar spine measured by	Bone mineral density quantification in femoral neck, hip, or lumbar spine.

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Test definition	Unique Biomarker Name
densitometry for risk prediction in a general population of 1. **Multiple sclerosis (MS)** OR 2. **Parkinson's disease**	
Quantification of Cu brain levels analysed by immunoturbidimetric assay and Schosinsky o-dianisidine eCp assay to detect susceptibility to **Alzheimer's disease (AD).**	Copper (Cu) concentration within the brain
Quantification of Cu serum/plasma levels analysed by immunoturbidimetric assay and Schosinsky o-dianisidine eCp assay to detect susceptibility to **Alzheimer's disease (AD).**	Copper (Cu) serum/plasma levels
Cortical thickness measurement using structural magnetic resonance imaging (sMRI) in individuals with Subjective Cognitive Decline (SCD) to predict clinical progression to **MCI** or **Alzheimer's disease**.	Cortical thickness
Quantification of excessive tonic electromyographic activity in isolated rapid eye movement sleep behaviour disorder (iRBD) patients to predict the clinical progression to **Parkinson's disease**.	Excessive tonic electromyographic muscle activity
Genetic test for the IL2RA gene to predict risk of **Multiple sclerosis (MS).**	IL2RA gene
Genetic test for the IL7R gene to predict risk of **Multiple sclerosis (MS).**	IL7R gene
Quantification of nigrostriatal dopaminergic impairments though dopamine transporter imaging (DAT) in putamen level imaging using different techniques in subjects with isolated rapid eye movement sleep behaviour disorder (iRBD) to predict the clinical progression to **Parkinson's disease**.	Nigrostriatal dopaminergic impairments
Quantification of non-Ceruplasmin Cu levels using immunoturbidimetric assay and Schosinsky o-dianisidine eCp assay to predict the risk of **Alzheimer's disease (AD).**	non-Ceruplasmin Copper (Cu) levels

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Test definition	Unique Biomarker Name
The measurement of the omega-3 index in blood in a general population to predict the risk of developing **Alzheimer's disease (AD)** and **all-cause dementia**.	Omega-3 index
PC[16:0/22:5(4Z,7Z,10Z,13Z,16Z)] phosphatidylcholine quantification in plasma by Ultra-Performance Liquid Chromatography/Quadrupole Time-of-Flight Mass Spectrometry/Mass Spectrometry (UPLC/Q-TOF-MS/MS) for the detection of **Alzheimer's disease (AD)** in a general population.	PC[16:0/22:5(4Z,7Z,10Z,13Z,16Z)] phosphatidylcholine in plasma
Measurement of pTau in CSF by enzyme-linked immunosorbent assay (ELISA) to predict the clinical progression of Subjective cognitive decline (SCD) to **Mild cognitive impairment (MCI)** or **Alzheimer's disease (AD)**.	Phosphorylated tau in cerebrospinal fluid
ptau181 quantification with Single Molecule Array Technology (SIMOA) or Meso Scale Discovery (MSD) platform to predict Amyloid Beta Positron Emission Tomography (Aβ-PET) status for the early diagnosis of **Alzheimer's disease (AD):** 1. in a general population OR 2. in patients with Mild cognitive impairment (MCI).	ptau181
Quantification of tTau in CSF by enzyme-linked immunosorbent assay (ELISA) to predict the clinical progression of Subjective cognitive decline (SCD) to Mild cognitive impairment (MCI) or **Alzheimer's disease (AD).**	Total tau in cerebrospinal fluid (CSF)
Stearic acid quantification in plasma by Ultra-Performance Liquid Chromatography/Quadrupole Time-of-Flight Mass Spectrometry/Mass Spectrometry (UPLC/Q-TOF-MS/MS) for the detection of **Alzheimer's disease (AD)** in a general population.	Stearic acid in plasma

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Test definition	Unique Biomarker Name
Quantification of vitamin B12 (cobalamin) in serum to predict the risk in a general population of 1. **Multiple sclerosis (MS)** OR 2. **Parkinson's disease.**	Vitamin B12 (Cobalamin) in serum
Genetic testing for the Vitamin D Receptor (VDR) gene to predict risk of **Alzheimer's disease (AD).**	Vitamin D Receptor (VDR) gene
Quantification of 25-hydroxyvitamin D in serum for risk prediction in a general population of: 1. **Alzheimer's disease (AD)** OR 2. **Multiple sclerosis (MS)** OR 3. **Parkinson's disease**	25-hydroxyvitamin D in serum
White matter hyperintensities measured using structural magnetic resonance imaging (sMRI) in a population with Subjective Cognitive Decline (SCD) to predict clinical progression to **mild cognitive impairment (MCI)** or **Alzheimer's disease (AD).**	White matter hyperintensity

None of these had any evidence from guidelines, HTA or CEA studies. Tests including biochemical biomarkers such as vitamins, lipids or proteins can also be found in the table. Among the latter are the different isoforms of the beta-amyloid protein (Aβ42 and Aβ42/Aβ40 ratio) and the tau protein (total tau, phosphorylated tau and ptau181). These are known biomarkers for Alzheimer's disease and are used in a diagnostic context, although their application in earlier stages of the disease is under study but this use has not yet been supported in guidelines. Finally, there were specific biomarkers in test definitions that considered several diseases, mainly vitamins and bone mineral density.

Primary prevention versus secondary prevention

In general, the tests included both primary and secondary prevention, and most were focused on disease prediction or risk/susceptibility detection. In the case of prediction, as with the tests with evidence in the previous section, some were focused on predicting progression from a related neurodegenerative condition to AD.

Conclusion

There were no tests with evidence supportive of clinical utility identified. For most of the evidence found in the searches, these were unrelated to the disease or biomarker in terms

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of primary or secondary prevention and most results considered the biomarkers as tests for diagnostic purposes.

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3.3.4 Genetic search results – neurodegenerative diseases

In the previous section, we searched for the genes identified as biomarkers in a test. In order to broaden our search for evidence of the role of genetic testing in the personalised prevention for neurodegenerative diseases, we did a general search in the same databases, with the strategy outlined below. As in the other group of diseases, this is complemented by a specific search for polygenic scores and their possible applications.

Biomarker name: Genetic test

Biomarker context and test definition: Genetic testing in the context of neurodegenerative diseases prevention involves the analysis of an individual´s DNA to identify specific genetic variations, mutations, or biomarkers that may indicate an increased risk of developing these diseases. The primary goal is to assess a person´s genetic predisposition to certain types of neurodegenerative diseases to implement targeted preventive measures. Genetic testing can provide insights into an individual´s susceptibility, allowing personalised and proactive strategies to reduce or manage the risk of developing neurodegenerative diseases.

Results of the search: Genetic test was searched for in guideline central and TRIP databases for all the selected neurodegenerative diseases. In Guideline Central 117 results were obtained but only 6 were under the filter of Neurology. Some related guidelines were found but these did not contain any recommendations for the use of genetic testing for the relevant diseases. In TRIP database 14 guidelines were found in Europe and eight in the UK. Only two guidelines fitted the test definition, and none of them provided useful data on clinical utility of genetic testing for these diseases.

Evidence of clinical utility for the test

Evidence 1: Essential tremor in Adult patients [A]
This Guideline was published in Guideline Central in May 2021 and states that genetic testing is not currently available.

Evidence 2: Genetic testing in childhood. Guidance for clinical practice [B]
This report offers guidance to UK healthcare practitioners on genetic testing in children, discussing social and legal implications to encourage best practice. It explores different scenarios in regard to genetic testing for late-onset complex diseases, including Alzheimer's disease, but does not make a specific recommendation for these diseases. The British Society for Genetic Medicine and the Royal College of General Practitioners both advise caution on Direct to Consumer genetic testing results, emphasising the importance of carefully considering the clinical utility of such tests and raising ethical concerns, particularly when applied to children.

Conclusion
Genetic testing is not recommended for the diseases that are evaluated in this report.

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Search terms used for this biomarker

Guideline Central search terms used: genetic test

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: (("alzheimer" OR "dementia" "lewy body" OR "vascular dementia" OR "frontotemporal dementia" OR "parkinson" OR "multiple sclerosis" OR "amyotrophic lateral sclerosis") AND ("genetic test") AND ("prevent" OR "screen" OR "early diagnos")) from_date:2013

A. Reiling Ott K, Shill H. Essential Tremor in Adult Patients. Published online August 8, 2023. https://eguideline.guidelinecentral.com/i/1380755-essential-tremor-advisory-ietf/0?

B. Clarke A, Hall A, Hart R. Genetic testing in childhood. Guidance for clinical practice. R Coll Pathol Br Soc Genet Med. Published online 2022. https://www.rcpath.org/resourceLibrary/genetic-testing-in-childhood-pdf.html

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3.3.5 PRS search results – neurodegenerative diseases

Neurodegenerative diseases predominantly arise from multifactorial origins. Typically, these conditions exhibit polygenic inheritance patterns shaped by the interaction of genetic predisposition and environmental factors. The PGS serves as an estimate of an individual's vulnerability to a particular disorder, calculated from the weighted correlations of single nucleotide variants or risk variants commonly revealed through genome-wide association studies.

Biomarker name: Polygenic risk score

Biomarker context and test definition: Polygenic risk scores for early detection and risk prediction for the potential prevention of neurodegenerative diseases

Results of the search:

In Guideline Central two guidelines were found, but they were not relevant to the test definition. In the TRIP database 76 guidelines were found, of which one was relevant and registered.

Evidence of clinical utility for the test

Evidence 1: Genetic testing in childhood. Guidance for clinical practice [A] (see also section 3.3.4)

This guideline discusses the enormous interest in recent years in the application of genetic and polygenic risk scores for chronic diseases such as Alzheimer´s disease. With regard to polygenic risk scores, it remains uncertain whether some useful clinical applications will emerge for the modest shifts in risk estimates that they generate for complex diseases, given low fraction of disease heritability that they can explain. The guideline affirms that PRS have little or no demonstrated clinical utility and so would often be regarded as not appropriate in a healthcare context, especially for pre-implantation or prenatal testing of fetal polygenic risks.

Conclusion

No evidence identified to support the use of PRS for neurodegenerative diseases.

Search terms used for this biomarker: polygenic

Guideline Central search terms used: polygenic

TRIP Advanced "ALL of these words" OR TRIP PICO Outcome: (("alzheimer" OR "dementia" OR "lewy body" OR "vascular dementia" OR "frontotemporal dementia" OR

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"parkinson" OR "multiple sclerosis" OR "amyotrophic lateral sclerosis") AND ("polygenic") AND ("prevent" OR "screen" OR "early diagnos”))

A. Genetic testing in childhood. R Coll Pathol. Published online 2022. https://www.rcpath.org/resourceLibrary/genetic-testing-in-childhood-pdf.html

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3.3.6 Neurodegenerative diseases discussion

Most of the biomarkers for neurodegenerative diseases were biochemical and among them, the best known and most frequently found were of beta-amyloid and tau proteins. Similarly, other biomarkers searched for neurodegenerative diseases were vitamins (vitamin d and vitamin b12), lipids (fatty acids, 16-a-hydroxypregnenolone, stearic acid, phosphatidylcholine), and metals (copper), among others. No guidelines have been found that recommend the use of these tests for prevention. Among imaging biomarkers, machine and deep learning strategies can be considered a promising area of research to identify early stages of the disease. However, unless they are clearly standardised, it is difficult to evaluate their clinical utility.

Genetic testing for neurodegenerative diseases might also provide the opportunity for prevention. In the case of dementias such as Alzheimer's disease, approximately 25% of cases are estimated to be familial [37]. Moreover, other dementias such as Lewy body dementia and frontotemporal dementia are other significant types of neurodegenerative disease with genetic causes. In the case of Parkinson´s disease, around 5-10% of the cases are attributable to pathogenic variants in single genes [37]. Demyelinating diseases are also potential beneficiaries of genetic testing, among which we can find multiple sclerosis and amyotrophic lateral sclerosis, in the latter 5-10% of the cases are familial [38, 39]. However, although there is enough evidence to support the importance of genes in the onset of neurodegenerative diseases, no guidelines have been found recommending their use [37].

In terms of specific diseases, Alzheimer's disease is the most frequent cause of dementia, but prevention strategies are limited. With regard to polygenic risk scores (PRS), they have been used in neurodegenerative diseases mostly to study the genetic overlap between neurodegenerative diseases or to try to evaluate their association with age at onset or other clinical features. Their inclusion in preventative models or as preventative tools is still in the research phase.

Several of the biomarkers identified were focused on beta-amyloid protein and tau protein. Abnormal amyloid beta deposition starts decades before the onset of Alzheimer´s disease, while tau aggregation and accumulation begin in the neocortex just a few years before the onset of cognitive impairment [40]. However, our search did not find any guideline that recommended their use.

Another aspect is the population in which a test is applied. In many cases, research is done in individuals with mild cognitive impairment or subjective cognitive impairment, with the aim of predicting progression to Alzheimer's disease. In this way, it is possible to identify those who are likely to develop the disease and those whose condition remains stable. The only test that has been found with evidence does include these different populations, but, again, the guideline indicates that it is still under research.

Regarding other dementias (vascular dementia, Lewy body disease and frontotemporal dementia), the only test related to the three dementias together with Alzheimer's disease was Omega-3 index, but no evidence was found to support its use.

Parkinson's disease, as in Task 2.1.1 was the condition with the second highest number of biomarkers following Alzheimer's disease. More specifically, five biomarkers were

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considered. In Parkinson´s disease, there is a need for reliable biomarkers to assess and quantify the clinical consequences of the disease and to support the clinical evaluation of the efficacy of new preventive strategies [41].

In terms of population, some test definitions include the REM sleep behaviour disorder (iRBD) population to be able to use the biomarker to predict those subjects who evolve into established Parkinson's disease, which is called phenoconversion. However, no guideline, HTA or CEA considered this specific subpopulation.

In the case of multiple sclerosis, an earlier and more accurate identification of the risk for the disease or for the diagnosis could provide a prevention or delay of typical manifestations. Numerous studies have concentrated on the prodromal phase, revealing quantifiable neurological deficits as well as investigating the levels of various molecules. Likewise, this is a disease in which there is a special relevance of the interaction or exposure to other factors such as vitamin D, which is one of the few tests that was included in our analysis [42]. As in the previous case, we did not find any evidence recommending the use of any of these tests in prevention.

Some biomarkers/tests focused on primary prevention (i.e., bone mineral density in femoral neck, hip or lumbar spine measured with densitometry; quantification of vitamin D as 25-hydroxyvitamin D; vitamin B12 in serum) appeared in several guidelines, but in these cases the recommendations were focused on dietary patterns and not on their use as biomarkers of risk of disease. Thus, although there is a known relationship between vitamins and disease risk, their application in clinical practice requires further evidence.

In conclusion, much research that has been done in neurodegenerative diseases but the tests identified are still far from being applied in clinical practice. Considerable research is still required to address this gap.

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4 Discussion

4.1 Study methods

We have developed a framework and search strategy to identify evidence for the assessment of the clinical utility of tests incorporating novel biomarkers for the personalised prevention of common non-communicable diseases (NCDs). The strategy is disease process agnostic and can be expanded for use outside of the three use cases presented here – cancer, CVD and neurodegenerative diseases. It is flexible to enable users to start at different points depending on the data they are interested in. Searches for guidelines, HTAs or CEAs can be done separately.

We have used different databases to undertake a comprehensive assessment of the sources of evidence. In order to establish the level of omission for the databases used in our search strategy we undertook certain checks including searches for inclusion of already identified key documents. All the searches identified the correct documents, and we believe that our method is unlikely to have missed key documents. We believe that this search methodology can reliably identify the correct documents.

4.1.1 Limitations of study methods

Our search strategy does have limitations, primarily that guidelines, HTAs and CEAs will be missed if they are not captured in the databases used. However, these databases are the most comprehensive available. If a test can be defined for a biomarker, then the search methodology can be used.

Our searches were limited to English language publications only. It is possible that guidelines applicable to particular populations of interest were missed if they were published in languages other than English.

The searches were conducted to capture recently – the last 15 years – published guidelines, which were more likely to provide the current evidence landscape and assessments of clinical utility. Using this strategy, it is possible that some evidence published earlier in time might have been missed.

4.1.2 Database considerations

TRIP was found to be the most comprehensive of the databases and also had the best search functionality. TRIP gives access to ongoing clinical trials and over one million full-text articles. It provides a subscription 'Pro' service which enabled us to perform more in-depth searches with improved capabilities over the open access version. This increased the robustness of our search strategy giving confidence we could identify documents relevant to our searches.

All the databases used were live and being regularly maintained and updated by the developers. A timeframe cut off for searches was used. Furthermore, the database versions need to be taken into account. During the CVD investigation, TRIP changed their advanced search function to include only a Boolean style search. This potentially improved the sensitivity and specificity of the search but was implemented after the CVD searches were completed but before those for neurodegenerative disease and cancer were performed.

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The other databases used did not offer Boolean search options or the opportunity to refine the specificity of searches. Additional filtering was not possible within some open access databases, therefore the results returned were general, and not necessarily related to the disease of interest or population. Some results returned did not mention the biomarker of interest.

Finally, it should be noted that conducting a search of this type requires subscriptions to TRIP, which could restrict access. We also found that a few guidelines were behind paywalls, which reduces their access to researchers and decision makers.

4.1.3 Observations/considerations regarding the search strategy

There are a number of practical considerations when undertaking searches of this type. In some papers, it was not always possible to identify a test definition. The ability to define a test definition relies upon the clear presentation of the purpose of a biomarker's use. For example, one scoping review identified in Task 2.1.1 captured all biomarkers for detection of large vessel occlusions (CVD) and therefore this paper included biomarkers at different stages of development, used in different populations and for different purposes [43]. The presentation of the results in this paper meant it was not possible to define a test for any of the biomarkers resulting in their exclusion from the process. Greater awareness of the importance of a test definition could support better evidence generation for clinical utility assessment and to focus research to support translation.

There are some caveats to consider for this type of search strategy. We developed a specific framework to assess evidence of clinical utility since an appropriate one was not identified. This situation may stem from the complexity around the definition of clinical utility. Depending on the disease group, assay, technology being used, and its purpose, the assessment of clinical utility can differ. In some cases, evidence of clinical utility will be in the form of improved test specificity, but in others it may come in the form of a less invasive sampling method or a new assay which could speed up time-to-result, simplify analysis or make use of the test in a new setting.

Nomenclature is a key factor to consider when carrying out searches. Biomarkers may be known under multiple names or variations of acronyms, one example from CVD is NR2-peptide that can also be found under the name N-methyl-D-aspartate. Therefore, advance planning to gather all variations of nomenclature is crucial to ensure an accurate search is performed in databases that will not always index these variations.

The specificity of the searches varied depending upon the search terms and the indexing in the databases used. In some cases, particularly where the biomarker had multiple uses in different disease processes, the search would identify many results with no relevance to the disease of interest, e.g., the characterisation of microbiome profiles in cancer. Careful planning and trialling of search terms should be performed in advance to reduce unnecessary work to identify extraneous results.

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4.2 Study findings

4.2.1 Disease specific findings

For all three disease groups, the majority of searches did not retrieve any type of evidence regarding the clinical utility of tests using the biomarkers of interest. This finding was not unexpected given that the searches focussed on biomarkers that we found in Task 2.1.1, which aimed to identify novel biomarkers that might be used in the personalised prevention of disease. Many of the tests using these biomarkers are still in the research phase. This means that their analytical and clinical validity might not yet be established and it is too early to consider implementing them in clinical settings.

Among the evidence prioritised for Task 2.1.2 using the above methodology, genetic biomarkers represented a large proportion of the papers, for example 50% of the prioritised cancer biomarkers were genetic related. This reflects the depth and breadth of genetic research, particularly in cancer, where underlying genetics play a key role in the development of many cancer types. In cancer, most of the biomarkers with evidence for clinical utility were also genetic.

In most cases, the genetic biomarkers were specific variants identified in association studies. These associations are frequently weak and would not have significant predictive value, therefore these genomic markers are unlikely to be carried forward as individual tests. This was supported by guidelines identified for cancer genetic biomarkers, where the clinical utility of the genetic biomarkers was reliant on them being used in a panel together and not individually. Our search strategy used gene names when the biomarker was associated with a variant within a gene rather than the variant themselves. This was because available guidelines on genetic tests may not always specify variants, rather the genes or gene regions in which they are found.

In CVD, the tests with evidence of clinical utility consisted of imaging or predictive model biomarkers. Many of these tests modified or updated well established methods such as utilising CAC scoring in previously overlooked populations or by adding further biomarkers to established integrated risk models that have multiple risk factors. The genetic tests identified explore known associations and the research studies investigated their use in different contexts or clinical situations. Other biomarkers were associated with known metabolic pathways and studies were attempting to determine if there was a link to disease.

Similarly, in neurodegenerative diseases only one test involving imaging biomarkers had evidence, which was not supportive of clinical utility. Established imaging techniques such as structural magnetic resonance imaging (sMRI) were investigated for use in different populations to improve detection in complex disease processes.

4.2.2 Genetic tests and polygenic risk scores additional searches

In order to obtain a broader understanding of the clinical relevance of genetic biomarkers in prevention, these biomarkers were also evaluated as a group. Similarly, an additional search for evidence of clinical utility focused on the use of PRS in prevention was conducted.

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We identified that for various cancers genetic testing is already incorporated in the clinical management of people who have high-risk germline mutations. For CVD, guidelines recommending genetic testing for conditions such as cardiomyopathies and arrhythmias, that have a strong genetic basis, are well established. Genetic testing is generally recommended for patients already diagnosed with or suspected of having an inherited CVD, or in those with a high risk due to a previously identified pathogenic variant being in the family. No guidelines were identified supporting genetic testing for the neurodegenerative conditions considered.

Whilst there is considerable research in the development and use of polygenic scores, for those cancers with guidelines identified in our literature search which address PRS (for breast, prostate, and liver cancers), they are not yet recommended as risk-assessment tools in clinical practice. For CVD, we have found guidelines suggesting that PRS may hold potential in predicting CVD risk. However, these guidelines emphasise the need for additional evidence to fully support their use. In neurodegenerative diseases, we found no guidelines supporting the use of PRS in clinical settings.

We believe these additional evidence searches provide valuable insights into the current position of the use of genetic tests and PRS in prevention for the three disease groups. In particular, our results highlight a significant evidence gap for their implementation particularly for genetic tests in neurodegenerative diseases and the use of PRS in prevention interventions across all three disease groups.

4.2.3 General results considerations

There are a number of considerations around the general applicability and relevance of the results of this study.

First, in many of the test definitions investigated, the target population was not stated. In most cases, it could be inferred that this was a general population based upon the cohorts used in the original research papers. In these situations, consideration is needed regarding the transferability of the test to populations other than the population in which it was originally developed and validated. For example, does the test definition and/or population consider the health differences across populations (e.g. diabetic population) or patient groups? In some cases, the same biomarker was investigated across a general population but also in populations such as those with chronic kidney disease or Type 2 diabetes. It was sometimes then the case that evidence regarding the general population was identified but not for the specific patient groups.

Second, research and by extension test development, is impacted by the lack of ethnic diversity in research cohorts. During our searches, outside of the west European cohorts, test definitions were only developed for Asian, Chinese and Oceanian populations. This will have an impact on the evidence available for the assessment of the clinical utility of such tests in the more diverse populations in many European countries.

There will be a degree of clinical judgement and adjustment required when clinicians use guidelines to inform their practice. Clinical guidelines need to balance specificity to their population against flexibility to support appropriate clinical judgement. Clinical guidelines require ongoing curation and updates for a number of reasons, including: advances in

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medical knowledge, technological advancements, changes in treatments or diagnostic tests, safety concerns about the interventions, changing demographics and clinical epidemiology. In this study, we have not made a judgement on the quality of the guidance found.

Our scoping review of biomarkers in research carried out in Task 2.1.1 found a large number of biomarkers, of which very few had established evidence for clinical utility as demonstrated in this study. While there are a number of reasons behind the research to clinical practice translational gap, a focus on ensuring that evidence for clinical utility is considered and gathered at every step of the research and test development process will expedite the appropriate implementation of tests into clinical practice.

As we outlined in the introduction to this report, assessment of clinical utility is complex and can vary depending on the range of factors considered including the context of use, disease of interest, cost of the test and its ease of use. A pre-requisite to clinical utility is evidence of analytic validity – the demonstration of assay performance in the laboratory setting, – and clinical validity, the demonstration of test performance characteristics in a clinical setting. Impact on personal, ethical, legal, and social outcomes can also be considered, as well as information on the impact on workflows, feasibility of test delivery and cost effectiveness. Finally, evidence of impact on clinical decision making and clinical outcomes are needed. Each of these factors should be considered to provide a comprehensive view of the clinical utility of tests, and each are critical for assessing the overall effectiveness and appropriateness of tests in public health and healthcare settings.

4.2.4 Recommendations for the research agenda for prevention

Based on our findings and analyses, we recommend the following actions for improving research efforts in the area of personalised prevention:

1. Research funders should continue to fund high quality biomarker research and the necessary translation and implementation studies for biomarkers and the tests in which they are used.
2. Research funders should encourage the evaluation and validation of biomarkers and the tests in different subpopulations (i.e., age groups; gender; population group) to improve information for personalised prevention approaches.
3. Research funders should consider developing and implementing a prioritisation approach to support the necessary implementation and translation research for biomarkers/tests for prevention purposes.
4. Researchers in the field of biomarkers should ensure that their research clearly contributes to a test definition for further translational research and prevention purposes.
5. Research activity should continue to identify biomarkers in areas such as genomics, epigenomics, proteomics, metabolomics, microbiomics and exposomics, integrating this information to enhance their usefulness for personalised prevention in terms of the development of risk prediction models.
6. Research in the use of machine learning algorithms should be supported as this can improve biomarker validation efforts and the development of risk prediction models.

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a PeRsOnalized Prevention roadmap for the future HEalThcare
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However, standardisation in research methods and reporting, is needed to translate these results into clinical practice.

7. Greater efforts and resources are needed to integrate electronic health records (EHRs) into research, for example risk modelling using large-scale omics datasets linked with EHRs and other sources of data including socio-demographic and environmental exposures. Appropriate research study designs incorporating these elements will be needed to improve preventive strategies.
8. Research funders should also promote the consideration of other domains (e.g. social, behavioural, environmental) to allow a more complete perspective of the usefulness of any proposed test or biomarker in terms of personalised prevention from the public health perspective.

5 Conclusion

We have completed Task 2.1.2 which was to undertake further analysis and research to establish the level of evidence for the clinical utility for personalised prevention of the biomarkers identified in Task 2.1.1 for the three disease areas: cancer, cardiovascular diseases and neurodegenerative diseases. In addition, we have undertaken further research to investigate the use of genetic testing and polygenic risk scores for prevention purposes in these three disease areas. Our results demonstrate significant evidence gaps and lack of translation of promising biomarkers for prevention. This requires urgent attention in order to accelerate the development of improved prevention interventions and programmes for the European population.

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a PeRsOnalized Prevention roadmap for the future HEalThcare
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6 Appendix

6.1 Table of Acronyms

2D two dimensional

2DM two-dimensional mammography

3D three dimensional

AAA abdominal aortic aneurysm(s)

ACOG American College of Obstetricians and Gynaecologists

ACMG American College of Medical Genetics and Genomics

AD Alzheimer's disease

AFP alpha-fetoprotein

AI artificial intelligence

ALDH-2 aldehyde dehydrogenase-2

ASCVD atherosclerotic cardiovascular disease

AWMF Association of The Scientific Medical Societies in Germany

BAC breast arterial calcification

BIMC Bayesian Inference Malignancy Calculator

BIRADS radiologist breast density assessment

BMI body mass index

CAC coronary artery calcium

CAD coronary artery disease

CEA cost-effectiveness analysis

CHARGE-AF Cohorts for Heart and Aging Research in Genomic Epidemiology model for atrial fibrillation

CKD chronic kidney disease

CMR cardiovascular magnetic resonance

COPD chronic obstructive pulmonary disease

COPD-LUCSS + DLCO model COPD-Lung Cancer Screening Score + diffusing capacity for carbon monoxide prediction model

CPG clinical practice guidelines

CRC colorectal cancer

CRP C-reactive protein

CSF cerebrospinal fluid

CT computed tomography

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a PeRsOnalized Prevention roadmap for the future HEalThcare
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CTA computed tomography angiography
CVD cardiovascular disease
DAT dopamine transporter imaging
DBT digital breast tomosynthesis
DCP des-gamma-carboxy prothrombin
DKG German Cancer Society
DKH German Cancer Aid Foundation
DRE digital rectal exam
EBV-VCA Epstein-Barr virus viral capsid antigen
ECG electrocardiography
EHRs electronic health records
ELISA enzyme-linked immunosorbent assay
EPI ExoDx prostate IntelliScore
EU European Union
EAU European Association of Urology
EAS European Atherosclerosis Society
EHRA European Heart Rhythm
ESC European Society of Cardiology
ESMO Europeans Society for Medical Oncology
FDA U.S. Food and Drug Administration
FEV1% percent-expected-forced expiratory volume in 1s
FH familial hypercholesterolaemia
fidART flicker-induced dilatation of retinal arterioles
fPSA free prostate specific antigen
GLP-1 glucagon-like peptide-1
GRADE Grading of Recommendations, Assessment, Development, and Evaluations
HCC hepatocellular carcinoma
HCM hypertrophic cardiomyopathy
HDL high-density lipoprotein
HF heart failure
HGPC high-grade prostate cancer
HNPCC hereditary nonpolyposis colorectal cancer
HNR Heinz Nixdorf Recall study

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Hs-CRP high-sensitivity C-reactive protein
HTA health technology assessment
IHD ischemic heart disease
IgA Immunoglobulin A
IgE Immunoglobulin E
IgG Immunoglobulin G
IgM Immunoglobulin M
INTEGRAL Integrative Analysis of Lung Cancer Etiology and Risk
iRBD isolated rapid eye movement sleep behaviour disorder
IS ischemic stroke
LCDRAT Lung Cancer Death Risk Assessment Tool
LCRAT Lung Cancer Risk Assessment Tool
LDCT LDCT
LDL-C low-density lipoprotein cholesterol
LLP Liverpool Lung Project
lncRNA long non-coding RNA
LV left ventricle/ventricular
LVH left ventricular hypertrophy
MACE major adverse cardiac events
MCI mild cognitive impairment
MESA Multi-Ethnic Study of Atherosclerosis
MI myocardial infarction
MiPS Michigan Prostate Score
MiRNA micro-RNA
MPS MyProstateScore
mRNA messenger RNA
MS Multiple sclerosis
MSD Meso Scale Discovery
MRI magnetic resonance imaging
NAFLD non-alcoholic fatty liver disease
NASH non-alcoholic steatohepatitis
NCD non-communicable diseases
NICE National Institute for Healthcare and Excellence

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a PeRsOnalized Prevention roadmap for the future HEalThcare
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NIHR National Institute for Health Research

NLST National Lung Screening Trial

P2PSA [-2]pro-prostate specific antigen

OPG osteoprotegerin

PAD peripheral artery disease

PanCan Pan-Canadian Early Detection of Lung Cancer Study

PCa prostate cancer

PCA3 Progensa Prostate Cancer Antigen 3

PD Parkinson's disease

PET positron emission tomography

PGS polygenic scores

PHI Prostate Health Index

PIB-PET [^{11}C] *N*-methyl [^{11}C] 2-(4'methylaminophenyl)-6-hydroxy-benzothiazole positron emission tompgraphy

PKUPH Peking University People's Hospital

PLCO Prostate, Lung, Colorectal and Ovarian model

PRECeDI Personalised medicine for disease prevention consortium

PRS polygenic risk score(s)

PSA prostate specific antigen

RECODe The Risk Equations for Complications of Type 2 Diabetes

RCC renal cell carcinoma

RCT randomised control trial

rt-qPCR reverse-transcriptase quantitative polymerase chain reaction

SCD Subjective cognitive decline

SGLT-2 sodium-glucose transport protein 2

SIMOA Single Molecule Array Technology

SNP single nucleotide polymorphism

SPN solitary pulmonary nodule

SRIA Strategic Research and Innovation Agenda

sMRI structural magnetic resonance imaging

sRANKL soluble receptor activator of NF-κB ligand

T2DM type 2 Diabetes Mellitus

TNSF-SQ Taiwanese non-smoking female Lung Cancer Risk prediction models using genetic information and simplified questionnaire

PROPHET
a PeRsOnalized Prevention roadmap for the future HEalThcare

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tPSA total prostate-specific antigen

UK United Kingdom

UKPDS UK Prospective Diabetes Study

UPLC/Q-TOF-MS/MS Ultra-Performance Liquid Chromatography/Quadrupole Time-of-Flight Mass Spectrometry/Mass Spectrometry

USPSTF United States Preventive Services Taskforce

UTR Untranslated region

WHO World Health Organization

VA Veteran's Affairs

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6.2 Glossary of General Terms

Prevention: reduction of the likelihood of developing a disease, sustaining an injury, or experiencing an unfavourable outcome. This study includes both collective (e.g., population screening) and individual (e.g., individual risk stratification) preventive measures [44].

Primary prevention: activities that are carried out before the appearance of a disease or pathology [44].

Secondary prevention: Individual and community measures to reduce the prevalence of diseases through early detection and prompt intervention, focusing on individuals with the disease in its preclinical phase, with manifestations that are not apparent but that allow its detection [11, 44].

- Population screening: it is the practice of early detection of the disease that is actively offered to defined population groups susceptible to presenting the disease that do not have symptoms and have not sought medical care [11].
- Early clinical detection: aimed at people who go to health services for various reasons, including symptoms that could be related to the disease being detected or even expressly demand the practice of the detection test. It reinforces population screening and diagnoses cases that the screening indicates as suspicious [11].

Risk: Probability of a negative or positive event occurring in a specified population during a particular period of time. It is commonly measured in epidemiology and clinical research by the cumulative incidence and incidence ratio [11].

Stratification: The process of or result of dividing a sample population into subsamples according to specified criteria, such as age groups, socioeconomic status, risk groups, etc. [11].

Cancer diseases: Conditions where abnormal cells, in a specific part of the body, divide without control and can invade nearby tissues and produce distant metastases. Included in the C00-C97 codes of the ICD-10 classification [45].

Cardiovascular diseases: A type of disease that affects the heart or blood vessels of which only some pathologies will be selected based on their magnitude and severity. Intermediate outcomes prior to disease onset of the included pathologies may also be considered as proxies for the latter.

Neurodegenerative diseases: Disorders that affect the brain as well as the nerves found throughout the human body and the spinal cord included in codes G00-G99 of the ICD-10 classification [45]. Intermediate outcomes prior to disease onset of the included pathologies will also be considered as proxies for the latter

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6.3 List of Figures and Tables

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