Assessing the impact of developments in genetic testing on insurers’ risk exposure

Daniela Rodriguez-Rincon, Sarah Parkinson, Lucy Hocking, Hamish Evans, Emma Hudson, Katherine Morley on behalf of the Cambridge Centre for Health Services Research
This report presents the final report of a study commissioned by the Association of British Insurers to assess the potential impact of developments in genetic testing on insurers' risk exposure.

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Preface

This report presents the final report of a study for the Association of British Insurers to assess the potential impact of developments in genetic testing on insurers’ risk exposure. The report describes the background to the study, the methodology used and the key findings of the study and sets out areas of interest for potential future research.

This research, prepared for the Association of British Insurers, was subject to RAND Europe’s rigorous evaluation and quality review process, and does not imply endorsement of any product, position or service. RAND Europe independently conducted the analyses performed and presented in this report, and had full editorial control.

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Summary

Interest in genetic testing has significantly increased since the mapping of the human genome in 2003, offering great insight into disease risk. NHS Genomic Medicine Centres have now been rolled out across England and offer tests from the NHS National Genomic Test Directory [1, 2], with partner organisations in Wales, Scotland and Northern Ireland [3]. Thus, genetic testing is becoming part of routine clinical care and this will increase in the future [4].

Why genetic tests are relevant to insurance

Predictive genetic tests that provide an individual with information about their future risk of developing health conditions could have negative or positive impacts on the insurance industry, depending on how the information these tests provide is used. By giving individuals additional information about their future health genetic tests could exacerbate existing information asymmetry between insurers and consumers – a situation in which the consumer has more information about their health risks than the company providing them with insurance. If individuals at high genetic risk of becoming ill or dying are more likely to apply for insurance without sharing this information with the insurer and enabling them to account for it in insurance premiums, this is known as anti-selection or adverse selection due to information asymmetry.

This may lead to increased costs for the insurer if it results in an unanticipated increase in claims, particularly for high-value insurance policies. It may be further exacerbated if people identified as being at low risk are less likely to apply for insurance compared to the general population. If this happened on a large scale, the number of claims made by insured people would be much higher than anticipated and could make the insurance market unsustainable. In the long term, this may then lead to an increase in premiums for customers if insurers are not able to assess health risk accurately.

However, genetic tests results could have a positive impact if they make insurance products affordable for more consumers. This could occur if genetic test results indicate someone with a family history of a health condition is actually at low genetic risk of developing the condition, or if genetic test results lead to individuals engaging with interventions that reduce their risk of developing a health condition. Data from genetic tests could also enable insurers to better characterise individual- and population-level risk of morbidity and mortality, and thus reduce the overall cost of insurance for the population.
Code on Genetic Testing and Insurance

Currently in the UK, insurers’ use of information from genetic tests is outlined in the Code on Genetic Testing and Insurance, a regulatory structure agreed on by the UK government and members of the Association of British Insurers (ABI) in 2018 [5]. The Code is binding on members of the ABI, but non-members can also sign up. Insurers who have signed up to the Code only consider clinical predictive genetic tests in specific circumstances. Any predictive genetic tests undertaken while conducting scientific research, or genetic tests of blood relatives, are not in scope. Currently, the only situation in which someone must disclose genetic information to an insurer is if they have had a predictive genetic test for Huntington’s disease (HD) and they are applying for a life insurance policy worth over £500,000. Therefore, this only applies to a very small number of those applying for insurance and it means anyone can apply for up to £500,000 of life insurance cover without disclosing any predictive genetic test result.

The Code is reviewed every three years in a joint process by the government and the ABI to account for changes in the genetic testing landscape and the insurance market. The aim of the review is not to change how insurers use genetic test information, but rather to understand whether there have been substantial changes to either the genetic tests available to individuals or to the insurance market that warrant a revision of how the Code is applied.

Against this background, the Cambridge Centre for Health Services Research (CCHSR), a collaboration between RAND Europe and the University of Cambridge, was commissioned by ABI to conduct a study to help assess the potential impact of predictive genetic testing on insurers who provide life, health and critical illness protection.

Study aim and overview

This report presents the results from an initial piece of research designed to develop a framework for evaluating the risk of negative impacts on the insurance industry arising from genetic tests that predict future risk of developing a health condition (i.e. not genetic tests that are used to confirm that someone has already developed a condition). The framework takes into account the characteristics of predictive genetic tests (e.g. how many genetic variants are included and how well the test predicts future risk), as well as behavioural factors (e.g. how much do people value the information they can obtain from taking a test and how do they use it). The framework is intended to provide a common, transparent approach for evaluating whether a specific condition for which a predictive genetic test is available presents an additional risk to the insurance industry, either currently or in the future, and for understanding the key factors that influence this. The framework may inform the review of the current Code and support the identification of areas where more in-depth and/or UK-focused research could be of use in understanding this topic.

We used an iterative approach to the development of the framework presented in this report, which included the following stages:

1. Developing a first draft of the framework based on a review of literature on the evaluation of genetic tests, followed by an internal research team workshop.
2. Refining the framework through:
   a. Incorporation of results from a Rapid Evidence Assessment (REA) of how individuals who receive genetic test results for genetic conditions use this information, and the impact of this on healthcare providers and the insurance industry.
   b. Incorporation of feedback from experts in the fields of genomics and insurance on the framework, their views on how the field may develop over the next five to 10 years and the impact this may have on clinical care and the insurance industry.
   c. Application of the framework to genetic tests for six groups of exemplar conditions—Huntington's disease, breast and ovarian cancer, familial hypercholesterolaemia, Lynch syndrome, coronary heart disease and frontotemporal dementia—to illustrate a range of possible scenarios in terms of: (i) test characteristics; (ii) condition characteristics; (iii) interventions available; and (iv) likelihood of change over the next five to 10 years.

Findings from the rapid evidence assessment and expert interviews

How individuals who receive genetic test results for genetic conditions use this information is a key element of the framework and broader considerations of the impact of genetic testing on healthcare and the insurance industry. For this reason, we conducted an REA, a rapid but robust and reproducible way of reviewing the literature, to answer three questions:

• Why are people who take predictive genetic tests motivated to do so?
• Do people who undertake predictive genetic testing disclose results to their healthcare providers or insurers, and what are the impacts of predictive genetic testing in terms of insurance-related behaviour?
• Does receiving genetic information about future disease risk lead to a change in health-related behaviours?

We found some evidence to suggest that health-related reasons, such as health monitoring or adopting behaviours to decrease health risks, are important among those who seek out genetic testing, although many also engage in testing due to an interest in ancestry. We also found that while the majority of people who take genetic tests report an intention to share their results with healthcare providers, only a minority do so in practice. The literature on disclosure of genetic test results to insurers and the impact of receiving test results on insurance-related behaviour is limited. Although there is some indication of the potential for information asymmetry and adverse selection, the extent of the issue is unclear. Based on our interviews with experts in the fields of genetic testing and genomics, decisions about purchasing insurance do not appear to be the primary concern when engaging with genetic testing in the UK due to universal healthcare access, relatively low levels of health insurance purchase and implementation of the Code governing the use of these data by insurers.

In terms of the impact of genetic test results on behaviour change, we found that people receiving information that they are at increased genetic risk for developing a condition express motivation to engage in lifestyle changes to reduce this risk. However, the evidence for behaviour change occurring in practice is more mixed and appears to vary depending on the type of health condition and types of lifestyle changes required to reduce risk. Both the motivation to engage with
healthcare professionals and the actual engagement with healthcare professionals after receiving a genetic test were found to be low, and evidence regarding intended and actual engagement with disease screening and uptake of pharmacological and surgical interventions was mixed.

**Framework for the evaluation of the impact of genetic tests on the insurance industry**

The framework covers four overarching questions for consideration when assessing whether a genetic test may be relevant to the UK insurance industry in relation to risk estimation, information asymmetry and potential for anti-selection:

1. How useful is a particular genetic test for characterising the risk of developing a condition?
2. How many people take the test?
3. What is the impact of the condition in terms of the length and quality of life of people who develop it?
4. What is the potential for reducing the risk of developing the condition and managing its effects if it develops?

The factors related to these questions (outlined below in Table 1) interact and should be considered together when assessing a predictive genetic test.

**Table 1 Outline of framework for the evaluation of genetic tests**

<table>
<thead>
<tr>
<th>Factors relevant to framework area</th>
<th>Description of the factors</th>
<th>Relevance to the framework and the insurance industry</th>
</tr>
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<tbody>
<tr>
<td>How useful is the test for characterising the risk of developing a condition?</td>
<td></td>
<td>For tests available through the NHS, adoption in clinical practice is a proxy for clinical utility. However, assessing this link for tests provided by direct-to-consumer (DTC) companies may be more difficult as they may not be equivalent to those used by the NHS.</td>
</tr>
<tr>
<td>Clinical utility</td>
<td>Extent to which clinically relevant action can be taken based on the results of the test. For a test to have clinical utility, it must have demonstrated analytic validity, and scientific and clinical validity.</td>
<td></td>
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<tr>
<td>Alternative information sources</td>
<td>Extent to which predisposition to a given condition can be estimated using information other than genetic test results (e.g. family history or lifestyle).</td>
<td>If information from a genetic test provides a more accurate estimate of disease risk than these alternatives, or can improve risk estimation when combined with them, there is risk of information asymmetry for insurers.</td>
</tr>
<tr>
<td>Factors relevant to framework area</td>
<td>Description of the factors</td>
<td>Relevance to the framework and the insurance industry</td>
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</tr>
<tr>
<td>How many people take the test?</td>
<td>Community’s desire for genetic tests, which is influenced by whether the community benefits from the tests, as well as personal preferences and autonomy. Community in this context could be the general population, or those who are already at elevated risk due to family history or other factors.</td>
<td>Interest in genetic testing varies by age, education, knowledge of genetics, family history of genetic conditions and the integration of genetic tests into the healthcare system. Consideration of uptake in certain subgroups may be important for insurers if the subgroup is more likely to have insurance or more likely to be at risk of developing a condition.</td>
</tr>
<tr>
<td>Societal acceptability</td>
<td>Value of the information to the person being tested.</td>
<td>Personal utility of a genetic test will vary by person and by the characteristics of the condition being tested for. Personal utility of a genetic test is likely to increase as capacity of genetic tests to estimate risk improves and/or as the range and effectiveness of interventions for a condition increase.</td>
</tr>
<tr>
<td>Personal utility</td>
<td>How a test is accessed in terms of public (or private) medical system or DTC provision, eligibility criteria and the degree of clinical support both before and after testing.</td>
<td>Under current NHS guidance, most individuals will only be referred for a genetic test if they are suspected by a clinician of having a certain condition, either due to symptoms or family history. Genetic testing for many conditions in the absence of family history or other indicative factors and without interaction with healthcare providers is available via DTC testing. However, most DTC tests that are currently available do not have the same clinical utility as those offered in the NHS.</td>
</tr>
<tr>
<td>Factors relevant to framework area</td>
<td>Description of the factors</td>
<td>Relevance to the framework and the insurance industry</td>
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<tr>
<td>Cost of the test</td>
<td>Upfront financial investment undertaken by an individual in purchasing the genetic test.</td>
<td>The impact of test cost on uptake may be limited to tests not currently available via the NHS, and to individuals who do not meet NHS criteria for test access but perceive the personal utility to be high and have the ability to pay. If the technological costs decrease but access to genetic tests via the NHS remains limited to those who meet eligibility criteria, the risk of information asymmetry and associated anti-selection may increase substantially.</td>
</tr>
<tr>
<td>Penetrance</td>
<td>Likelihood that specific forms of a gene or genes (genetic variants) will be expressed in an individual and lead to development of the condition.</td>
<td>For a condition to be important for medical underwriting in insurance, it must have high penetrance. Capacity to assess penetrance depends on the type of conditions being tested. For example, for conditions determined by a large number of genes, the likelihood of developing the condition is more challenging to estimate.</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Age range in which the condition being predicted by the genetic test usually occurs.</td>
<td>The age of onset of a condition may affect anti-selection of insurance. For example, an individual at risk of an early onset condition may purchase insurance earlier than they may have otherwise done or, conversely, an individual at risk of a late onset condition may delay seeking insurance. Also, consumers may be able to anti-select if they have reason to believe that they are subject to a late onset condition that has presented no symptoms at the time of purchasing insurance.</td>
</tr>
<tr>
<td>Prognosis and morbidity</td>
<td>Prognosis is the time from development of the condition to death, while morbidity refers to the consequences for quality of life and/or the health of the individual who develops the condition.</td>
<td>Conditions with a high mortality rate (combined with a lack of effective treatment) are important for insurance underwriting, but the time from diagnosis to death and the health state during those years are also important as there may be implications for employment and health and/or social care, which may also have implications for insurance.</td>
</tr>
<tr>
<td>Prevalence</td>
<td>Proportion of people within a population who develop the condition being tested.</td>
<td>Conditions with high prevalence may have a large overall financial impact on insurers. However, conditions with low prevalence may also have an impact if people who are at high genetic risk are disproportionately likely to purchase insurance or make an insurance claim.</td>
</tr>
</tbody>
</table>
Factors relevant to framework area | Description of the factors | Relevance to the framework and the insurance industry
--- | --- | ---
**What is the potential for reducing the risk of developing the condition and managing its effects if it develops?**

**Potential for risk reduction and/or treatment**
- Risk reduction includes interventions delivered before an individual develops symptoms of a condition or when they have developed early symptoms and prevention may still be possible.
- Treatment strategies are interventions delivered to people after they have developed a condition, with the aim of reducing its impact on their quality of life and/or life expectancy.
- Risk reduction approaches may lead to overdiagnosis and overtreatment, a situation in which an asymptomatic individual is identified as being at high risk of a condition that would not have discernible consequences for them during their lifetime but triggers clinical interventions, which may have an impact on critical illness and medical insurance providers.
- Conditions for which treatments are available may have implications for medical insurers, while those for which there is no effective treatment present the greatest risk in terms of life insurance.

**Effectiveness and engagement**
- Risk reduction effectiveness is the capacity of a strategy to reduce an individual's risk of developing a condition.
- Treatment effectiveness is the effect on an individual's prognosis and morbidity.
- Engagement is the extent to which an individual uses an intervention, which may affect its effectiveness.
- The effectiveness of an intervention and the extent to which individuals engage with it are key influences on whether risk reduction or management are feasible for a health condition. Many insurance companies encourage their customers to lead healthy lifestyle and offer financial rewards for doing so (e.g. reduced premiums or discounts on services), but evidence for the impact of risk reduction strategies following genetic tests is mixed and dependent on the condition tested for.

**Intervention costs**
- Financial investment required to carry out an intervention.
- If an individual is identified as being at genetic risk of a condition, the cost of providing them with risk reduction interventions and treatment if the condition develops will have an impact on the risk a genetic test poses to the insurance industry. This risk will be greatest when the cost of treatment is high, particularly in the absence of preventative interventions.

**Reflections and areas for future research**
We developed a framework for evaluating the risk of negative impacts on the insurance industry arising from genetic tests, taking into account characteristics of genetic tests as well as behavioural aspects that influence uptake of genetic tests in the population. This framework is
intended to provide a common, transparent approach for evaluating whether a specific condition and associated genetic test presents a potential risk to the insurance industry.

Following an expert review, we applied the framework to six groups of conditions selected to explore a range of different predictive genetic test scenarios: Huntington’s disease, breast and ovarian cancer, familial hypercholesterolaemia, Lynch syndrome, coronary heart disease and frontotemporal dementia. Doing this application highlighted that assessment of the risk to the insurance industry presented by genetic tests and associated conditions is affected by a complex interplay of factors related to the genetic test itself, engagement with testing, the number of genetic variants that affect the development of the condition and how strongly they influence risk, the capacity for reducing risk and the cost of treatment. For some conditions (breast and ovarian cancer, Lynch syndrome and frontotemporal dementia), genetic testing is limited by current knowledge of the genetic variants that increase risk of developing these conditions. For all the conditions we examined, with the exception of Huntington’s disease, the effect that the major genetic variants currently identified have on an individual’s risk of developing a condition is variable. This means that not everyone who carries one of the genetic variants will go on to develop the condition in question. Similarly, not all cases of these conditions are due to a known genetic variant. This makes precise characterisation of individual risk for developing these conditions following a genetic test result challenging.

The key factors that may change the risk presented by genetic tests and associated conditions are better characterisation of genetic risk for these conditions or the development of interventions for conditions where treatment options are currently limited (Huntington’s disease and frontotemporal dementia), particularly if this increases test uptake. For some conditions (familial hypercholesterolaemia and coronary heart disease), if genetic testing is used for risk stratification to target interventions that reduce health risks earlier, this may lead to the condition presenting less of a risk to insurers over time.

With the exception of coronary heart disease, the genetic tests we investigated are only used in UK clinical practice for people already suspected as being at elevated risk due to family history or presentation of symptoms. Therefore, access to these tests is generally limited to people already at elevated risk of developing these conditions and use by the general population is currently low. Although genetic tests for some conditions (breast and ovarian cancer, frontotemporal dementia and coronary heart disease) can be accessed via DTC genetic testing companies, the tests offered are not as comprehensive as those offered clinically and their utility is generally much lower. Any future changes to test access, either due to changes in NHS eligibility or development of DTC offerings, are likely to play a key role in determining whether genetic tests present risks to the insurance industry.

Potential areas for future research

This research has identified a number of important gaps in the evidence base, most of which could be addressed as part of future research studies to provide additional insight on the potential impact of genetic testing on the UK insurance industry:

- **Availability of data on genetic tests and conditions.** Making a definitive assessment of the potential risk a genetic condition presents to the insurance industry is complex and limited by the availability of current data from the UK population on test characteristics, availability and
update, prognosis and morbidity, and intervention effectiveness and adherence. The advent of clinical polygenic risk scores\(^1\) combined with whole genome sequencing (WGS)\(^2\) may make this even more challenging. Addressing this limitation is beyond the capacity of any individual researcher; it will improve as the field develops and if/when specific tests are incorporated into clinical practice. However, the framework outlined in this document can act as a guide for determining the areas and types of information that warrant monitoring to understand how the risk to insurers may change as research develops further.

- **Lack of research on UK samples.** Research on the impact of genetic test results on insurance-related behaviours and behaviour change is limited, heterogeneous and has many methodological limitations (e.g. sampling from specialised subsections of the population, unstandardised outcome measurements, lack of appropriate comparator groups). Most importantly in a UK context, most research has not been conducted with samples from the UK population, so making inferences about motivations for engaging with genetic testing, how people would use the information, and any risk of information asymmetry and adverse selection is difficult. Findings from our expert interviews also indicated that the fundamental differences in healthcare and insurance between the UK and other countries, particularly the US where most research has been conducted, mean that findings from other countries are not easily extrapolated to the UK. Conducting research using UK samples on uptake of and motivations to use genetic tests, and the potential impact of this information on decisions regarding insurance and engagement in risk-reducing behaviours, would be beneficial in addressing this gap.

- **Uncertain likely impact of developments in genetics and genomics on the healthcare and insurance sectors.** The ways in which information about the risk of developing a genetic condition is accessed by individuals and incorporated into clinical practice in the NHS are likely to change over the next five to 10 years. While our expert interviewees all agreed that uptake of genetic information, and the breadth of information available, are both likely to increase, there was less consensus on what the implications of this might be for the healthcare and insurance sectors. How this might affect the risk presented by individual genetic tests to the UK insurance industry is therefore unclear. This uncertainty could be reduced to some extent through research collating the perspectives of key stakeholders (a small amount of which was undertaken for this report) and modelling variation in the elements of the framework outlined here to identify combinations of characteristics of a genetic test, or thresholds these characteristics would need to meet, before a test potentially presents a risk of information asymmetry and adverse selection.

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1. Polygenic risk scores summarise the estimated effect of many genetic variants on an individual's risk of developing a health condition or trait.
2. Whole genome sequencing involves determining the whole DNA sequence of an individual genome, including the identification of many different types of genetic variants.
Table of contents

Preface III
Summary V
Figures, tables and boxes XVII
Abbreviations XIX
Acknowledgements XX

1. Background to the study 1
   1.1. Key motivations for this research 1
   1.2. Purpose and approach of the study 4

2. Methodological approach 7
   2.1. Draft framework development 7
   2.2. Refinement of the framework 8
   2.3. Strengths and limitations of the approach 13

3. REA of motivations for predictive genetic testing and its impact on health-related behaviours 15
   3.1. Assessment of the evidence base 15
   3.2. Health-related reasons are important motivations for people to get genetic tests, among other factors 17
   3.3. Many people are likely to disclose genetic tests results to healthcare providers, but the impact on the insurance sector is less clear 19
   3.4. While most people intend to make lifestyle changes after receiving genetic test results, this does not generally translate into making changes in practice 22
   3.5. Evidence for engagement with healthcare professionals after receiving genetic test results is limited, and the evidence for uptake of surgical and pharmacological interventions is mixed 24
   3.6. Summary and discussion 25

4. Expert perspectives on current and future developments in predictive genetic testing 27
5. Framework for evaluating the risks presented by genetic tests to the UK insurance industry
   5.1. How useful is the test for characterising the risk of developing a condition?
   5.2. How many people take the test?
   5.3. What is the impact of the condition in terms of the length and quality of life of people who develop it?
   5.4. What is the potential for reducing the risk of developing the condition and managing its effects if it develops?
   5.5. Application of the framework to a selection of conditions

6. Summary, reflections and suggestions for future research
   6.1. Findings and reflections
   6.2. Potential areas for future research

References

Annex A. Data collection template for the development of the draft framework
Annex B. Expert interview protocol
Annex C. Search Strategy for the REA
Annex D. Inclusion and exclusion criteria for REA
Annex E. Data extraction fields for the REA
Annex F. Reviewed studies for the REA
Figures, tables and boxes

**Figures**

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1</td>
<td>PRISMA diagram for rapid evidence assessment</td>
<td>10</td>
</tr>
<tr>
<td>Figure 2</td>
<td>Framework for assessing the potential risk presented by a genetic test and associated condition to insurers</td>
<td>44</td>
</tr>
<tr>
<td>Figure 3</td>
<td>Assessment of genetic test for Huntington’s disease</td>
<td>45</td>
</tr>
<tr>
<td>Figure 4</td>
<td>Assessment of BRCA1/2 genetic test for breast cancer – current assessment in colour; hypothetical future assessment in uncoloured shapes with dashed outlines</td>
<td>49</td>
</tr>
<tr>
<td>Figure 5</td>
<td>Assessment of genetic test for familial hypercholesterolaemia – current assessment in colour; hypothetical future assessment in uncoloured shapes with dashed outlines</td>
<td>54</td>
</tr>
<tr>
<td>Figure 6</td>
<td>Assessment of the genetic test for Lynch syndrome – current assessment in colour; hypothetical future assessment in uncoloured shapes with dashed outlines</td>
<td>58</td>
</tr>
<tr>
<td>Figure 7</td>
<td>Assessment of the genetic test for coronary heart disease – current assessment in colour; hypothetical future assessment in uncoloured shapes with dashed outlines</td>
<td>62</td>
</tr>
<tr>
<td>Figure 8</td>
<td>Assessment of the genetic test for frontotemporal dementia – current assessment in colour; hypothetical future assessment in uncoloured shapes with dashed outlines</td>
<td>65</td>
</tr>
</tbody>
</table>

**Tables**

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1</td>
<td>Outline of framework for the evaluation of genetic tests</td>
<td>VIII</td>
</tr>
<tr>
<td>Table 2</td>
<td>Interview participants for the study</td>
<td>12</td>
</tr>
<tr>
<td>Table 3</td>
<td>Framework summary</td>
<td>32</td>
</tr>
</tbody>
</table>
Table 4  Huntington's disease  46
Table 5  Breast and ovarian cancers  50
Table 6  Familial hypercholesterolaemia  55
Table 7  Lynch syndrome  59
Table 8  Coronary heart disease  63
Table 9  Frontotemporal dementia  66

Boxes
Box 1  Summary of REA findings on motivations to get genetic tests  17
Box 2  Summary of REA findings on whether people disclose results from genetic tests to healthcare providers and insurers  19
Box 3  Summary of REA findings on lifestyle changes related to genetic tests  22
Box 4  Summary of REA findings on engagement with healthcare following genetic testing  24
Box 5  Scopus search string (1)  99
Box 6  PsycINFO search string (1)  100
Box 7  Scopus search string (2)  101
Box 8  PsycINFO search string (2)  101
Box 9  Grey literature search string (1)  102
Box 10  Grey literature search string (2)  102
Abbreviations

ABI Association of British Insurers
CCHSR Cambridge Centre for Health Services Research
CHD Coronary heart disease
CRC Colorectal cancer
DES Diethylstilbestrol
DTC Direct-to-consumer
EOCHD Early onset coronary heart disease
FH Familial hypercholesterolaemia
FTD Frontotemporal dementia
GP General practitioner
HD Huntington's disease
HCM Hypertrophic cardiomyopathy
LDL Low-density lipoproteins
LS Lynch syndrome
LYG Life-year gained
NGS Next generation sequencing
NHS National Health Service
ONS Office for National Statistics
PMI Private medical insurance
PRS Predictive risk score
RCT Randomised controlled trials
REA Rapid evidence assessment
UK United Kingdom
US/USA United States of America
VTE Venous thromboembolism
WGS Whole genome sequencing
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1 Background to the study

This report presents the results from an initial piece of research designed to develop a framework for evaluating the risk of negative impacts on the insurance industry arising from genetic tests that predict future risk of developing a health condition (i.e. not genetic tests that are used to confirm that someone has already developed a condition). The framework takes into account the characteristics of predictive genetic tests (e.g. how many genetic variants are included and how well the test predicts future risk), as well as behavioural factors (e.g. how much do people value the information they can obtain from taking a test and how do they use it). The framework is intended to provide a common, transparent approach for evaluating whether a specific condition for which a predictive genetic test is available thereby presents an additional risk to the insurance industry, either currently or in the future, and for understanding the key factors that influence this. In this chapter we describe the factors that provide the motivation for this research (Section 1.1) followed by a discussion of the purpose and approach of the study (Section 1.2).

1.1. Key motivations for this research

Access to genetic testing is increasing

Interest in genetic testing has significantly increased since the mapping of the human genome in 2003, offering great insight into disease risk. NHS Genomic Medicine Centres have now been rolled out across England and offer tests from the NHS National Genomic Test Directory [1, 2], with partner organisations in Wales, Scotland and Northern Ireland [3]. This has increased the range of tests available and as well as making all genetic tests more accessible [6]. The current focus of these tests, and the 100,000 Genomes Project, is rare diseases and cancer, and the primary objective is to reduce diagnosis time and inform treatment decisions and estimates of prognosis [7].

Although not currently covered by the National Genomic Test Directory, tests that estimate individual risk of developing common and/or complex conditions such as cardiovascular disease and neurological and psychiatric disorders may also become available in future [8-10]. These conditions can have a moderate to high impact on morbidity and mortality and estimates of

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3 Project established by Genomics England to sequence 100,000 genomes from around 85,000 NHS patients affected by a rare disease or cancer, transforming care by bringing advanced diagnosis and personalised treatments to those who need them.
future risk of these diseases may influence individual health-related behaviours, including the decision to purchase insurance [11]. Such predictive tests may be offered by the NHS as well as be available privately, particularly via direct-to-consumer (DTC) testing companies. The growing availability of genetic information as a result of this increase in testing could have significant consequences for healthcare delivery and for the insurance industry.

**Genetic tests that provide an asymptomatic individual with insight into their future risk of illness could have negative and positive impacts on insurers**

Insurers use risk data to calculate the likelihood that an event for which a person seeks insurance may occur. This information is used to assess the cost of an individual’s premium, in such a way that the more likely an event is, the higher the risk to the insurer and, as a result, the higher the cost of the premium [12]. Predictive genetic testing is a form of evidence that helps determine an individual’s risk of developing a condition, and therefore genetic test results could be used to determine the cost of the premium. Depending on how genetic information is used, it could have positive or negative impact on the insurance industry.

Negative impacts may arise if:

- Individuals identified as being at high genetic risk of becoming ill or dying are more likely to apply for insurance without sharing this information with the insurer and enabling them to account for this appropriately in the insurance premium. This situation, in which a consumer who is purchasing insurance and the company providing that insurance do not have the same information about the consumer’s level of risk, is known as anti-selection or adverse selection due to information asymmetry. This may lead to increased costs for the insurer if it results in an unanticipated increase in claims, particularly for high-value insurance policies. It may be further exacerbated if people identified as being at low risk are less likely to apply for insurance compared to the general population. If this happened on a large scale, the number of claims made by insured people would be much higher than anticipated and could make the insurance market unsustainable [13].

- Actuarial risk assessments based on data from genetic tests with poor predictive performance could result in individuals being charged higher premiums for insurance than is warranted based on their real risk of developing a condition (i.e. false positives).

Positive impacts may arise if:

- Genetic test results indicate an individual characterised as being at high risk of illness or premature death due to family history of an inherited condition is found to be at low genetic risk, making insurance more accessible to them.

- Following identification of an individual as being at high genetic risk, the person can proactively reduce that risk (e.g. through lifestyle changes, screening or treatment).

- Using data from genetic tests, insurers are better able to characterise individual and population level risk of morbidity and mortality, and thus reduce the overall cost of insurance for individuals.
Use of genetic test results by insurers is regulated by an agreement between the UK government and the Association of British Insurers

Guidance for UK insurers’ use of predictive genetic test information is outlined in the Code on Genetic Testing and Insurance [5]. The Code is binding on members of the Association of British Insurers (ABI), but non-members can also sign up. Insurers who have signed up to the Code only take predictive genetic test results into account in specific circumstances: currently, only if an individual has had a predictive genetic test for Huntington’s disease (HD) and is applying for life insurance over £500,000. However, consumers can voluntarily share results, and insurers can take them into account where it is in the applicant’s favour [14].

The Code is be reviewed every three years in a joint process by the government and the ABI. The aim of the review is not to change how insurers use genetic test information but to understand whether changes in the genetic testing landscape or the insurance market warrant a revision of how the Code is applied. This could mean changing the genetic tests or insurance products for which exclusions apply, but this will only be considered where [5]:

1. The increased risk of morbidity or mortality for those at high genetic risk is substantial and can be evaluated with a high degree of certainty.
2. The predictive genetic test has high analytical and clinical validity and clinical utility.
3. It presents a material risk of anti-selection that impacts on individual premiums, creating a negative financial impact on consumers and insurers if not addressed.

Whether a genetic condition and associated test presents a risk to insurers depends on a complex interplay between characteristics of the condition, characteristics of the test, human behaviour and the terms of the insurance contract

Rothstein [15] has outlined the characteristics of a genetic condition that create the potential for a negative impact on insurers. It must:

• Be adult-onset (otherwise the individual would already exhibit symptoms).
• Have high penetrance (meaning there is a high chance the genes are expressed).
• Have high absolute risk (e.g. an individual with high genetic risk will have a high likelihood of developing the condition).
• Have high relative risk (e.g. an individual with high genetic risk is much more likely than a person at low risk to develop the condition).
• Have a high mortality or morbidity rate and a lack of effective treatment.

For a genetic test to have an impact, it must provide substantially improved risk estimation, beyond that provided by non-genetic sources (including family history) [15]. For common complex conditions, meaningful use of test results is not straightforward; data on many genetic variants often needs to be combined with data on environmental factors (e.g. smoking status) and biomarkers (e.g. cholesterol levels) to calculate a predictive risk score (PRS) to estimate individual disease risk [16]. The incremental value of information from genetic tests, beyond that obtained from other sources, needs to be considered in the context of these factors [17].
In the UK context, availability of a genetic test for a condition outside the NHS, such as via DTC genetic testing, must also be considered. Under current NHS guidance, in most cases patients will only be referred for genetic testing if they have a family history or other indicators that mean a genetic condition is suspected, or particular types of cancer, which excludes predictive tests for individuals with unknown family risk [2]. However, testing for many conditions in the absence of family history or other indicative factors is feasible via the DTC market. Currently, individuals are not required to disclose results from genetic tests to insurers (except for HD and certain life insurance products), regardless of whether these are obtained via the NHS or DTC providers. If this were to change, DTC tests could present an additional risk to insurers as it would be up to the individual to disclose this information to healthcare and/or insurance providers, which could exacerbate information asymmetry and adverse selection.

As noted above, the impact of genetic testing on the insurance industry also depends on how people use the results from genetic tests and how many people engage with genetic testing. The evidence for the impact of genetic test results on changes in health-related behaviour is mixed; as such, a cause-and-effect relationship has not been conclusively identified [18-23]. Similarly, research on the impact of genetic test results on uptake of insurance, or whether people who are tested and then seek insurance reveal the results of their test, is currently inconclusive but is likely to vary by genetic condition [24-27]. There is growing public interest in taking genetic tests to predict the risk of developing a genetic condition, although interest depends on the cost of the test and whether results are returned to a doctor, as well as the education level, age and genetic knowledge of an individual [28-32]. Those who engage with genetic testing are reported to be equally interested in ancestry information, understanding genetic traits and knowledge of disease risk, although interest varies by the type of condition tested for [33]. However, not all individuals will necessarily be motivated to seek out this information; some may be deterred from engaging with genetic testing due to concerns that test results may have implications for insurance through risk classification and potential ‘genetic discrimination’ [34].

1.2. Purpose and approach of the study

The aim of this study was to develop a framework for evaluating the risk of negative impacts on the insurance industry arising from genetic tests, taking into account characteristics of genetic tests as well as behavioural aspects that influence uptake of genetic tests in the population. The framework is intended to provide a common, transparent approach for evaluating whether a specific condition for which a predictive genetic test is available could present a risk to the insurance industry, either currently or in the future. It is also intended to help understand the key factors that influence this. It may inform the review of the current Code and support the identification areas where more in-depth and/or UK-focused research could be of use in understanding this topic.

We used an iterative approach to the development of the framework presented in this report via the following stages:

1. Developed a first draft of the framework based on a review of literature on the evaluation of genetic tests, followed by an internal research team workshop.
2. Refined the framework through:
   
a. Incorporation of results from a rapid evidence assessment (REA) of how individuals who receive genetic test results for genetic conditions use this information, and the impact of genetic testing on healthcare and the insurance industry.

b. Incorporation of feedback from experts in the fields of genomics and insurance on the framework, their views on how the field may develop over the next five to ten years and the impact this may have on clinical care and the insurance industry.

c. Application of the framework to genetic tests for six groups of exemplar conditions that illustrate a range of possible scenarios in terms of: (i) test characteristics; (ii) condition characteristics; (iii) interventions available; and (iv) likelihood of change over the next five to 10 years.

Further details of the methods used can be found in Chapter 2. We present the findings from the REA in Chapter 3, followed by a summary of the expert interview findings in Chapter 4. The final version of the revised framework is presented in Chapter 5. The summary and final conclusions are presented in Chapter 6.
2 Methodological approach

In this chapter, we present the methodological approach taken for the conduct of this study. This study sought to understand the extent of the problem facing the insurance industry from genetic testing, in terms of asymmetry of information and anti-selection, and to determine the need for further in-depth research. To achieve this, we:

1. Developed a framework for evaluating the risk of negative impacts arising from a genetic test.
2. Conducted an REA on motivations for engaging with genetic testing and the impact of this information on behaviour.
3. Validated the evaluation framework and REA results via expert consultation.
4. Applied the framework to genetic tests for six categories of exemplar conditions (HD, breast and ovarian cancer, familial hypercholesterolaemia (FH), Lynch syndrome (LS), coronary heart disease (CHD) and frontotemporal dementia (FTD)) that illustrate a range of possible scenarios in terms of: (i) test characteristics; (ii) condition characteristics; (iii) interventions available; and (iv) likelihood of change over the next five to 10 years.

Based on the findings from this research, we have formulated recommendations for future research. Details of the four research stages are provided in the sections that follow.

2.1. Draft framework development

2.1.1. Desk research

To support the development of the framework, we conducted a high-level summary of current literature on the characteristics and evaluation of genetic tests, and the key factors of relevance to the insurance industry. We used a pragmatic targeted approach to searching, including snowballing. Data from included literature were extracted into structured data extraction template for summarising key findings from all sources (Annex A). We focused on identifying how the impact of genetic tests on the insurance industry may be determined by the key characteristics of:

• Genetic tests, including availability and uptake, analytical validity, clinical utility and validity, and comparison with existing risk estimation approaches.
• Genetic conditions, including onset, penetrance, prevalence, morbidity, mortality and healthcare costs.
• Therapeutic options, including availability of interventions designed to prevent or delay onset of a condition.
2.1.2. Framework development workshop

Using the summary of the literature, we convened an internal workshop with the study team to develop an initial framework for evaluating genetic tests for the risk of negative impacts on the insurance industry. In developing this framework, we have made the following assumptions:

- Available tests (including those available outside the NHS) have received, and continue to receive, necessary approvals for use.
- The recipient of the test result is expecting to receive a predictive risk estimate for a given condition; we are not addressing:
  - Diagnostic testing in symptomatic individuals.
  - Predictions for drug response or to personalise treatment for those who have developed a condition.
  - Genome-wide screening and incidental findings.

We also considered the feasibility of obtaining data to answer each question in the framework to determine which aspects would be most useful for monitoring important changes in the genetic testing landscape over time.

2.2. Refinement of the framework

The draft framework was refined through:

a. Findings from an REA of how individuals who receive genetic test results for genetic conditions use this information and the impact of genetic testing on healthcare and the insurance industry.

a. Feedback from experts in the fields of genomics and insurance through interviews and a cognitive walk through.

a. Application of the framework to genetic tests for six groups of exemplar conditions to assess its use in practice.

2.2.1. Rapid evidence assessment

To understand the implications of predictive genetic testing on the insurance sector in the UK, we conducted an REA to answer the following research questions:

1. Why are people who take predictive genetic tests motivated to do so?

2. Do people who undertake predictive genetic testing disclose results to their healthcare providers or insurers, and what are the impacts of predictive genetic testing in terms of insurance-related behaviour?

3. Does receiving genetic information about future disease risk lead to a change in health-related behaviours?

REAs are reviews of the literature that are robust and reproducible in their approach, but also make some concessions as compared to a systematic review to ensure that they are efficient in terms of time and resources required [35]. An REA includes four stages: literature search, literature screening, data extraction and synthesis. These are described in detailed in the sections below.
Search strategy

Academic literature
In order to identify relevant literature, we developed two search strings in collaboration with a professional librarian (one search string for Scopus and one for PsychINFO) focusing on insurance-related and health-related behaviours (Box 5 and Box 6 in Annex C). We then developed two additional searches (one for Scopus and one for PsychINFO) focusing on motivations to undergo predictive genetic testing (Box 7 and Box 8 in Annex C). The search was limited to articles published between January 2015 and January 2021, resulting in 747 articles. After removing duplicates, these searches resulted in 678 articles. Four additional journal articles were also identified through reviewing reference lists for relevant review articles, resulting in 682 unique academic journal articles.

Grey literature
We also searched two curated databases of grey literature: OpenGrey4 and Trip5. OpenGrey is an open access database of European bibliographic references to grey literature including technical/research reports, doctoral dissertations, conference papers and government publications. Trip is a clinical search engine designed to allow users to find high-quality evidence-based research. This includes journal articles but also other content types including images, videos, patient information leaflets, educational courses and news. As with the academic literature, we constructed two sets of searches, adapting the academic searches to the constraints of the grey literature databases. One set focused on insurance-related and health-related behaviours (Box 9 in Annex C) and another set focused on motivations to undergo predictive genetic testing (Box 10 in Annex C). The grey literature searches resulted in 64 unique articles.

Screening
Once the literature search was completed, articles captured by the search were subject to title and abstract screening to determine their selection for the study. Article selection was based on a set of predefined inclusion and exclusion criteria relating to publication year and language, country of residence of study population, intervention studied, comparison group, outcomes measures and study design (for further details see Annex D).

Title and abstract screening
The academic and grey literature searches described above resulted in 746 articles (682 from the academic literature), all of which were screened by title and abstract. Grey literature articles were screened by a single researcher given the small number (64 in total) and the fact that the inclusion/exclusion criteria were easier to apply. Due to the large number of academic articles and the breadth and complexity of the content, a first stage of screening was undertaken by two researchers (SP and KM) in a blind double screen aimed at ensuring that all relevant articles were captured. The researchers reviewed each title and abstract and assigned a rating of ‘include’,

4 http://www.opengrey.eu/
5 https://www.tripdatabase.com/
‘exclude’ or ‘maybe’ for each article without knowing how the other reviewer rated the article. For articles that were excluded, a short reason was provided.

Screening was undertaken using Rayyan, a web application for reviews [36]. After screening all articles based on title and abstract, the results of the screening were unblinded. Articles for which reviewers assigned different ratings were discussed until consensus was reached, and in cases of disagreement a third researcher (DR) with experience in genetics was consulted to assist with decision making. This stage resulted in 79 articles continuing to full-text screening and 667 articles being excluded, for an inclusion rate at this stage of approximately 10.6%.

**Full-text screening**

All 79 articles that were selected for full-text screening based on title and abstracts were retrieved and reviewed to assessed based on the inclusion and exclusion criteria listed above. Three researchers (HE, LH and SP) conducted the full-text screening of the articles, with each article being reviewed by one researcher. Based on this screening, 54 of the 79 articles were included and extracted, while 25 articles were excluded. For each article that was excluded, a brief reason was noted. An overview of the number of articles that were identified, screened and included in the review is shown in Figure 1 below.

**Figure 1 PRISMA diagram for rapid evidence assessment**
Extraction

Primary research articles
A total of 54 articles were included for extraction. Three researchers (HE, LH and SP) conducted the extraction using an extraction template in Excel. The template captured information about the design of the study, the population included, the type and context of the genetic test (if applicable) and outcomes of each study relevant to answering each research question. Given the broad inclusion with regard to study designs (cohort, case/control, clinical trial and qualitative) and the large number of sources included, in-depth quality assessment of each study was not feasible. We therefore applied a set of qualitative and quantitative quality assessment questions that were applicable to all study designs, relating to the strengths and limitations of the study, clarity of population and setting, clarity of measures/outcomes/covariates, clarity of inclusion and exclusion criteria, and conflicts of interest. This information was combined with other extracted data, such as study design and sample size, to evaluate the contribution of each study to the evidence base. The extraction template was used to capture information as it was reported in each article and provided space for researchers to reflect on the relevance of the study to our research questions and other comments on the study. The fields of the extraction template are provided in Annex E.

Reviews
Systematic reviews were included in this study. However, the information extracted from reviews focused on what literature was reviewed and the findings from the systematic review and not the individual studies. One researcher (LH) extracted the two reviews that were included after full-text screening, adapting the Excel extraction template used for primary research articles and covering the same information. The detailed extraction template is provided in Annex E.

Synthesis and reporting of literature findings
Our approach to synthesising the literature is based on the guidance outlined by Varker et al. (2015) for evidence assessment and synthesis [35]. We reviewed the body of literature that addressed each research question and assessed the:

- Strength of the evidence base in terms of the quantity of studies, the quality and risk of bias and the level of evidence/study designs.
- Direction of the study results.
- Consistency of study results across study designs and populations.
- Generalisability of the evidence to the target populations of the included studies.
- Applicability of the evidence to the context of our review.

In organising the report, we drafted separate sections for each research question, with each section providing a narrative summary of the evidence (see Varker et al. 2015 for more details [35]). In order to avoid repetition, a section summarising the strength of the evidence base was drafted, which applies to studies relevant to all research questions in this review. The relevance of each study to the three research questions is reported in Annex F, along with information on the study population, intervention, comparator(s), condition(s) and outcome(s) for each study.
2.2.2. Expert review

Interviews

We conducted semi-structured interviews with seven key stakeholders (three were interviewed jointly) to validate the genetic test evaluation framework, in combination with the REA findings (see Table 2 below). Interviewees were selected based on their expertise in different aspects of genetic testing that are of relevance to this study, as well as their expertise with genetic testing and genomics in the UK.

Interviewees were provided with the draft framework and a summary of key REA findings prior to their interview in order to allow them time to reflect on the framework and provide feedback during the interview. We used a topic guide for the interview (Annex B) to ensure all key points were addressed while allowing for flexibility to explore aspects particularly relevant to the specific expertise of each participant. The topic guide covered feedback on both the framework and REA findings (including relevance to the UK context), but also asked interviewees to reflect on their views of how the field of genetic testing and genomics may develop over the next five to ten years. Interviewees were provided with a privacy notice where the purpose of the study and data collection were detailed. Interviews were conducted using Microsoft Teams and audio recorded for note-taking purposes.

Feedback from interview participants on the framework was directly incorporated, with explicit references included in the explanatory text. Interviewee reflections on future developments in genetic testing and genomics were summarised using a thematic analysis approach [37] and reported separately from the framework.

Table 2 Interview participants for the study

<table>
<thead>
<tr>
<th>Interviewee</th>
<th>Position and affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Christine Patch</td>
<td>Clinical Lead for Genetic Counselling at Genomics England</td>
</tr>
<tr>
<td>Professor Margaret Otlowski</td>
<td>Professor of Law at the Faculty of Law at the University of Tasmania and a Deputy Director of the Centre for Law and Genetics</td>
</tr>
<tr>
<td>DTC genetic testing industry</td>
<td>DTC genetic testing industry representatives6</td>
</tr>
<tr>
<td>Dr Jonathan Roberts</td>
<td>NHS Genetic Counsellor at Addenbrooke's Hospital and Researcher in the Society and Ethics at the Wellcome Sanger Institute</td>
</tr>
<tr>
<td>Professor Marcus Munafò</td>
<td>Professor of Biological Psychology and MRC Investigator, School of Psychological Science, Bristol Population Health Science Institute</td>
</tr>
</tbody>
</table>

Cognitive walk-through

We also conducted cognitive walk-throughs [38] of the framework (as applied to a selection of genetic conditions, see below) with two members of the ABI project team to collect feedback

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6 These interview participants requested that they remain anonymous. The interview was conducted with three individuals from the DTC genetic testing industry.
from experts from an insurance background. This provided perspectives on how different sections of the insurance industry (e.g. critical illness, private medical insurance (PMI) and life insurance) might utilise the framework in different ways, and where there may be variation in the priorities for the information contained in the framework itself. One member of the research team (EH) conducted these with each ABI team member separately using the cognitive walk-through with users approach, which combines the cognitive walk-through and concurrent think-aloud approaches to usability testing. Participants were provided with a version of the framework population with applied versions of the framework (see Section 2.2.3) and encouraged to discuss their thinking as they reviewed the document. The same researcher took notes that were then applied where relevant as part of the work undertaken to refine the framework at this stage.

2.2.3. Application of the framework to a selection of conditions

Based on the feedback received from the expert interviews and cognitive walk-throughs, we refined the framework through iterative internal team discussions. We then finalised the framework and associated guidance for its application. To demonstrate the application of the framework and provide some initial insight into the potential impacts of genetic testing on the insurance industry, we used the framework to evaluate a set of conditions and associated genetic tests.

The ABI project team provided a longlist of potential conditions of interest and a set of these were chosen to explore different possible scenarios regarding the types of genetic tests and conditions (i.e. variation in age of onset, morbidity and mortality, clinical specialty and available interventions). Both academic and grey literature were searched to identify documents that could provide answers for the framework questions for each condition. The information used in the application of the evaluation framework was summarised for each test, along with the conclusions drawn about the potential of the test to present a risk to the insurance industry and how this could change in future given plausible assumptions about technology development over the next five to 10 years.

2.3. Strengths and limitations of the approach

The key strengths of the framework development are the use of the existing literature to form an initial evidence base, followed by incorporating input from a range of experts to validate the framework and provide insight into which areas may be important to monitor as the field of genomics develops. Using a data collection template to compile information from existing frameworks to assess genetic testing allowed us to better identify the common areas of interest when assessing the utility of genetic tests as well as gaps to consider. Expert review provided us with insight into what the current factors impacting the use of genetic test and its impact on the insurance industry are, as well as how these have changed and might continue to change over the next five to 10 years. Therefore, expert review allowed us to develop a framework that can be adapted for use over time.

However, both the development and application of the framework were constrained by the limitations of the current literature. Most literature on the evaluation of genetic tests takes a clinical perspective, rather than an insurance perspective, and therefore required some adaptation when developing the framework. Applying the framework to the selected genetic conditions
was limited by the extent of the research that has been published up until the time of writing (10 May 2021). For some conditions, information needed to answer some framework questions was not accessible, out of date or not available for the UK population. This limited our ability to draw conclusions about the potential risk these conditions and the associated genetic tests may present to the UK insurance industry. However, it does highlight areas for future research and/or data gathering to monitor potential emerging risks.

The strengths of the REA lie in the screening process where all academic literature titles and abstracts were reviewed by two researchers independently to help ensure that the inclusion and exclusion criteria were applied consistently and that all relevant literature was included for extraction. We also used a structured approach to synthesis and reporting results to increase the robustness and transparency of our findings by providing information on the quality of the evidence base for each research question, the generalisability of study findings and their applicability to our target population. Lastly, we focused on empirical study results from a broad range of study designs and drew on both quantitative and qualitative evidence, which ensured our review encompassed a wide range of evidence.

However, there are several limitations to the REA. Firstly, we limited the search to studies published between January 2015 and January 2021. We used this timeframe because the general public’s familiarity with and understanding of concepts related to genetics has changed over the past decade [39], and focusing on more recent articles helped to ensure that our review findings were not unduly influenced by studies of early adopters of genetic testing. However, there may be relevant studies that were not included in this timeframe. Secondly, although the review is intended to gather evidence relevant to the insurance sector in the UK, there was limited evidence available from the UK and most evidence was available from the US (which has a substantially different healthcare and insurance systems). This limitation is reflected in our results and we acknowledge that it may limit the applicability of our review findings to a UK context. Lastly, we conducted a structured quality assessment of the included studies, but as this was an REA we did not conduct an in-depth formal quality review using a critical appraisal tool (e.g. AMSTAR2) as would be conducted in a systematic review. However, we critically reflect on the strengths and weaknesses of the evidence base throughout our findings and attempt to provide a balanced view of the evidence.
To understand the implications of predictive genetic testing on the insurance sector in the UK, we conducted an REA to answer the following questions:

1. Why are people who take predictive genetic tests motivated to do so?
2. Do people who undertake predictive genetic testing disclose results to their healthcare providers or insurers, and what are the impacts of predictive genetic testing in terms of insurance-related behaviour?
3. Does receiving genetic information about future disease risk lead to a change in health-related behaviours?

This chapter presents an assessment of the evidence base (Section 3.1), followed by the findings of the REA organised by research question (Sections 3.2 to 3.5), and a summary of the results (Section 3.6).

### 3.1. Assessment of the evidence base

To assess the quality of the evidence base for the REA (quantity, quality and level of evidence), the generalisability of the included studies and the applicability of the review findings to our population of interest, we drew on the work of Varker et al. (2015) [35]. Below, we discuss the evidence base for our review, taking into account all included studies. Where there are reflections around the evidence base for specific research questions, we have included this discussion throughout the report.

**Strength of the evidence base**

Overall, 54 studies were included in this review (see Annex D). Of the included studies, 24 were cohort design studies (including 1 quasi-experimental before and after study), 12 were case/control designs (including 6 randomised controlled trials (RCTs)), 14 were qualitative studies based on interviews and focus groups with small sample sizes, 2 were based on secondary analysis of data from RCTs and 2 were systematic reviews. For the primary studies (n=52) included in this review, the majority (n=38) collected data through surveys or questionnaires that measured self-reported behaviours and attitudes, and many studies (n=17) also collected data through interviews and focus groups. Although most data across studies was self-reported by
participants, a small number (n=7) of studies examined health records or other routinely collected data, or collected non-self-reported data using accelerometers or anthropometric measures.

We conducted a structured quality assessment of the included studies, but as this was an REA we did not conduct an in-depth formal quality review using a critical appraisal tool (e.g. AMSTAR2) as would be conducted in a systematic review. However, we critically reflect on the strengths and weaknesses of the evidence base throughout our findings and attempt to provide a balanced view of the evidence. We assessed each study in terms of the clarity of the population and setting, the clarity of measurements/definitions and outcomes and the clarity of inclusion and exclusion criteria. Nearly all included studies had clear descriptions of populations and settings, and clear measurements/definitions and outcomes. However, several studies were assessed as having poor clarity of inclusion/exclusion criteria in terms of how participants were selected for inclusion in the study. There were ten studies included in this review where the authors disclosed a potential conflict of interest (e.g. receiving funds from a company that provides genetic testing services, financial interest in companies and previous or current employment by a company). However, in general the quality of these studies with potential conflicts of interest was high and the overall risk of bias as a result of these for this review is low. There may, however, be a publication bias in that studies with null results may be less likely to be published than those with positive results, which is a risk for all reviews of this nature.

**Generalisability of included studies**

The samples of people collected in the included studies were often quite selective and may have had different attitudes, beliefs and behaviours around genetic testing than other populations. For example, many studies had samples that were drawn from populations of students, samples of people who had received genetic testing through DTC companies, who had agreed to take part in wider studies on genetics or genomics, or who had been part of early research cohorts on genetic testing. In general, study participants also tended to be more likely to be White, more likely to be female, with a higher income and more highly educated than the general population in the countries in which the studies took place. As such, some of the results from the included studies may not be generalisable to other populations. For certain populations, such as DTC customers, study results may be more generalisable, since the population that uses DTC genetic testing is already a selective population.

**Applicability of review findings**

This review has been conducted to collect information that is relevant to the insurance sector in the UK, thus making people in the UK who receive genetic test results the population of interest. Of the 54 studies included in this review, only seven7 studies were conducted using samples from the UK. The remaining studies included in this review were conducted with samples from the other countries: US, Canada, Australia or EU countries.8 Roughly half of the studies (26)9

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7 Including three studies that also sampled from other countries, along with the UK.
8 New Zealand was also included in this review, although no included studies were conducted with populations in New Zealand.
9 Including one study that also sampled from other countries, along with the US.
were conducted in the US, which has a substantially different insurance and healthcare system compared to the UK. However, the extent to which this lessens the applicability of study findings to the target population depends on the population the sample was drawn from and the topic and findings of each study. For example, DTC customers in other countries may be somewhat similar to those in the UK and findings regarding the factors that motivate people to get genetic testing and the impact of genetic testing on health-related behaviours may still be applicable to the target population of this review, provided that they are not closely linked with insurance and healthcare systems in their respective countries. Within this review, there were no studies that looked specifically at insured samples, so it is also unclear the extent to which findings apply to this population.

3.2. Health-related reasons are important motivations for people to get genetic tests, among other factors

**Box 1 Summary of REA findings on motivations to get genetic tests**

There were 24 studies included that provided information on why people who get predictive genetic tests are motivated to do so. There is evidence of moderate strength to suggest that health-related reasons, such as health monitoring and adopting behaviours or treatment to decrease health risk, are important in motivating people to seek out predictive genetic testing. Other reasons to get genetic testing include a general interest in genetic make-up, the ‘entertainment value’ of taking genetic tests and a desire to alert offspring and family members of potential risk for health conditions.

Although the cost of genetic testing has an impact on uptake, the evidence included in this literature review is not sufficient to know how other changes in external factors, for example in the healthcare system or insurance system, would impact the number of people seeking genetic testing for different conditions.

3.2.1. Health-related reasons motivate people to get genetic testing

The desire to have more knowledge about potential health risks was identified as an important motivation to seek out testing for both people that had received DTC testing [33, 40-42] and in other surveys where participants had not necessarily actively sought out genetic testing, but rather had received a test through participating in research cohorts or studies [43-47]. Obtaining information to inform adoption of behaviours or treatments to improve health, prevent disease onset or manage risk were also important motivating factors for DTC customers [33, 40-42] and in other survey studies [43, 45-48] and qualitative studies [49-53]. Several studies looked at interest in genetic testing for specific conditions and found that cancer (e.g. breast, prostate, skin and colon) [33, 42, 47], heart disease, Alzheimer’s disease and diabetes [33] were of particular interest for those receiving genetic testing. A few studies explicitly examined whether the actionability of information from genetic testing (i.e. whether it could be used to make decisions about risk reduction or treatment) may play a role in people’s motivation to take genetic tests. In a survey of DTC consumers, just over half of respondents reported that they had considered
whether there were health-related actions they could take in making a decision to get genetic testing [33]. This was the most important factor in deciding whether to take a genetic test that was identified in the study. In another study about genetic testing for breast cancer among women in the US, about three quarters of respondents reported that they would definitely or probably take a genetic test for breast cancer if it could provide information to guide decision making about risk reduction through medication (79%), diet and exercise (77%) or if they should undergo screening more often (74%) [48].

3.2.2. Perception and previous knowledge of risk can motivate people to get genetic testing

Some evidence suggests that individual perceptions of health and disease risk, along with previous knowledge of genetic risk (e.g. based on family history) can also be motivating factors to seek genetic testing. In several studies, lower levels of perceived health or higher levels of perceived disease risk were associated with more interest in genetic testing [33, 43, 48, 54]. Similarly, those with higher propensity to devote attention to their health and avoid bad health may be more likely to seek out information about genetic testing [43] and people with high dispositional optimism may be more likely to seek out results for conditions that are not medically actionable [55]. One study found that people's perception of their own disease risk was not associated with uptake of genetic testing, although it was conducted only with participants from a cohort of women at high risk of breast cancer [46] and it is unclear how generalisable this finding would be to a wider population. There is also evidence from a survey and qualitative studies to suggest that family history of a genetic condition can be a motivating factor for getting genetic testing [45, 53, 56, 57] and that people may be more interested in obtaining results for conditions that they already know occur in their family [51].

3.2.3. There is little evidence on whether insurance and financial planning are important motivating factors for those that undergo genetic testing

We found very few studies that explicitly investigated whether people who take genetic tests are motivated to do so for reasons related to insurance or financial planning; this REA did not include studies on whether concerns about insurance eligibility discouraged people from obtaining genetic tests. One study of women at high risk of breast cancer in the US found that the potential for genetic test results to impact on insurance eligibility influenced decisions around genetic testing for 34.2% of those that did not take up genetic testing and 46.6% of those that did, although it is unclear whether this would also apply to wider populations [46]. One other study discussed motivations around financial planning and found that 22% of German respondents and 9% of Italian respondents reported that they saw utility in genetic tests providing information to help with life planning related to personal finances [58]. However, this study was deemed to be of low quality.

3.2.4. Market acceptability and test characteristics affect willingness to get genetic tests

This review did not assess willingness to pay for genetic tests, although some studies provided insight into the extent to which cost has an impact on people's motivation to seek genetic testing. Evidence suggests that as cost decreases, more people will be interested in predictive genetic
Several included studies also found that convenience of the testing (e.g. being tested at home) [33] or invasiveness [60] was an important factor, with people being more likely to engage with tests that can be taken at home and/or are minimally invasive. The magnitude of the increase in risk for a condition that can be determined by a genetic test may also factor into decisions to undergo genetic testing. One study of a small sample of college students compared willingness to undergo testing under hypothetical scenarios where the test was able to predict a 10% versus a 2% increase in risk for schizophrenia (compared to a baseline risk of 1%), finding that more respondents would get tested if the test could predict a 10% increase in risk [61].

3.2.5. Other reasons such as ‘entertainment value’, interest and desire to alert offspring about health risks also motivate people to take a genetic test

Evidence suggests that concerns about offspring inheriting genetic conditions or a desire to warn offspring of potential genetic risks for a condition are important motivating factors for getting genetic testing [40, 42, 47, 49, 52, 62]. Although this review did not directly assess uptake in different populations, several studies suggested that people with children may be more likely to undergo genetic testing [42, 60]. Several studies also found that the potential benefit of genetic information for other family members can be a motivator [50, 58] and that some people may get genetic testing because they were told by family members about potential genetic risk for a condition [63].

Lastly, many people may undergo genetic testing for reasons such as a general interest in their genetic make-up (including ancestry) [40, 58, 63], which was mentioned as a reason in 98.1% of respondents in one study of those that sought out genetic testing [45], or due to the ‘entertainment value’ of genetic testing [45, 58].

3.3. Many people are likely to disclose genetic tests results to healthcare providers, but the impact on the insurance sector is less clear

Box 2 Summary of REA findings on whether people disclose results from genetic tests to healthcare providers and insurers

There were 18 studies included that provided evidence around the disclosure of genetic test results to healthcare providers and insurers, and the impact of genetic test results on insurance-related behaviour. The available evidence indicates that the majority of people report wanting to share test results with healthcare providers. However, evidence indicates that a smaller proportion of people actually report sharing this information once tested. Overall, a sizable minority of those that receive genetic test results are likely to share results with healthcare providers (mostly in primary care), particularly where results indicate potential risk for health issues.

There is little information available about disclosure of results to insurance companies and the impact of genetic test results on insurance-related behaviour (e.g. changing coverage levels and seeking out new insurance plans) and more evidence is needed in this area. The little evidence that is available points to a potential for information asymmetry and adverse selection, although the extent of the issue is unclear.
3.3.1. The majority of people report willingness to share genetic test results with healthcare providers and a sizeable minority actually do share this information

Based on studies that measured self-reported disclosure of genetic test results to healthcare providers, a larger proportion of people report that they would hypothetically discuss results with healthcare providers if they received genetic test results, or that they plan on sharing results with healthcare providers, as compared to those that report actually sharing information. In studies examining people's intentions of sharing genetic test results, between 62 and 88% of participants report planning to share results with healthcare providers or report they would share hypothetical results [42, 44, 54]. One study assessed different hypothetical situations around sharing genetic test results for women at high risk of breast cancer and found that 60% of women would share with their doctor if they were at below average risk, as compared to 81% of women if they were at above average risk [54]. In terms of actual sharing of results with healthcare providers, studies found that the percentage of participants who shared information ranged from 35 to 41% for those that received genetic test results from DTC tests [40, 44, 64], and from 12 to 53% for those that received genetic test results in research contexts [45, 65-69].

The percentage of people that shared results with healthcare providers varied between studies looking at different conditions, although the extent to which this is due to the specific condition or differences in study design is unclear. Unsurprisingly, more people reported sharing positive results (indicating a potential health issue) with healthcare providers as compared to negative results. For instance, one study found that of those receiving DTC genetic test results for venous thromboembolism (VTE), 41% that had the genetic variant associated with VTE shared the results with healthcare providers, as compared with only 7% that did not have the variant [64]. In an Australian study that provided people with information on their genetic risk of melanoma, 41% of those in the high-risk group shared information with healthcare providers, as compared to 16% in the average risk group and 12% of those in the low-risk group [66]. People mostly reported sharing results with primary care providers or general practitioners, although some also shared them with genetic specialists and other providers [40, 44, 45, 64].

Other contextual factors around genetic testing may influence whether people share results with healthcare providers. In one study comparing groups in the US that received a genetic test for free versus those that had a co-payment for their genetic test, those with a co-payment were more likely to share results with healthcare providers [70]. However, the study was of limited quality and it is unclear whether this finding would be generalisable to populations outside of the US given that it may be influenced by the US healthcare and insurance context.

This review investigated the sharing of genetic test results with healthcare providers due to the relevance of this information for the insurance sector and the possibility for insurers to access information recorded in healthcare records. However, information shared with healthcare providers may not always be available to insurers. Although no studies looked at genetic test results in health records, there is qualitative evidence to suggest that some people that receive genetic test results and discuss them with their healthcare providers may ask that their providers do not include this information in their health records due to fear of insurance or employment discrimination [63].
3.3.2. There is little evidence on disclosure of results to insurers and insurance-related behaviour

We only identified a few studies that investigated disclosure of genetic test results to insurers, although the little information that is available points to disclosure being low. The only quantitative estimate that is available is from a low-quality study based on a survey of Italian and German people who received genetic test results online from genetic labs, where just 1.6% of respondents reported results to insurers [58]. There is some evidence to suggest that disclosure to insurers may be associated with how people understand their results and their duty to disclose information. In a qualitative study in Australia of people receiving genetic test results for hypertrophic cardiomyopathy (HCM), disclosure to insurers depended on how the policy was worded and how an individual conceptualised a genetic test result indicating they were at increased risk [52]. Those who viewed themselves as having a pre-existing condition disclosed this to insurers, while those who viewed themselves as only being at risk of the condition did not [52]. Another qualitative study undertaken in Canada found that most participants thought that they did not have a duty to disclose genetic test results about breast cancer risk to obtain life insurance and that some reported lacking legal knowledge on whether this was required [57].

Few studies looked at whether receiving genetic test results has an impact on insurance-related behaviour (e.g. changing insurance policies, seeking out insurance and letting insurance lapse). An analysis of RCT data from the US revealed that 6% of participants who received genetic test results for Alzheimer’s disease made changes to their long-term care insurance and that those who received positive results (indicating higher risk) were more likely to report intentions to change insurance coverage (20% of those that tested positive as compared to 5% that tested negative) [71]. Another study provided a lower estimate, with just 0.4% of those receiving genetic test results (for a variety of monogenic diseases) in a research cohort context reporting making changes to their health, life, long-term care or disability insurance [45]. This highlights there is potential for insurance-related changes in response to genetic test results, but more research is needed in this area, particularly in the UK given the differences in healthcare and insurance systems as compared to the US.
3.4. While most people intend to make lifestyle changes after receiving genetic test results, this does not generally translate into making changes in practice

Box 3 Summary of REA findings on lifestyle changes related to genetic tests

There were 13 studies included that provided information on whether people intend to make lifestyle changes following results from a genetic test. Overall, the majority of the studies we included found that people receiving information that they are at increased genetic risk for developing a condition express motivation to engage in lifestyle changes (e.g. diet, exercise, etc.) that would reduce this risk. This appears to be the case regardless of the type of lifestyle change or the type of condition tested for (with the possible exception of cardiovascular conditions).

There were 15 studies included that provided information on whether people actually make lifestyle changes following results from a genetic test. Overall, the evidence for behaviour change occurring in practice (as opposed to in theory) is more mixed in comparison to the evidence for intention to make lifestyle improvements. Whether improvements to lifestyle are actually made appears to vary depending on the type of health condition and the types of lifestyle changes that are required to reduce risk (and the ease in which these can be undertaken).

3.4.1. Individuals appear to have a desire to improve their lifestyle after receiving genetic test results

The literature suggests that people are motivated to make improvements to their lifestyle (e.g. diet, exercise, sun protection, etc.) after receiving information on their genetic risk of developing certain conditions. This has been found in studies of individuals who have taken a genetic test [33, 42, 68, 71, 72] and research that presents participants with hypothetical genetic testing scenarios [47, 54, 60, 61, 73, 74]. This also holds true across different types of health conditions including Alzheimer’s disease, CHD, lung cancer schizophrenia and melanoma, although we did not find evidence for an increased motivation to improve lifestyle after a genetic test for cardiovascular risk and heart disease [53, 55]. However, both these studies noted certain contextual factors that may increase motivation to make lifestyle changes (e.g. support from friends/family, older age, more concrete genetic results, actionability of results or greater optimism). Overall, these findings suggest that motivation to improve lifestyle after receiving genetic test results generally does not depend on the type of health condition tested for. Similarly, these studies also found participants expressed motivation to improve a range of different lifestyle factors, including diet, exercise, sun exposure, substance use, dietary supplement intake or general (unspecified) lifestyle improvements.

However, all but one of these studies [68] exploring motivations to change lifestyle factors were not designed to examine differences in motivation between those receiving genetic test results and another group (e.g. people not receiving any information or receiving disease risk information based on non-genetic factors). The authors conducted a survey of individuals who received a
personalised risk assessment for melanoma based on self-reported family history and genetic test results to assess behavioural changes relating to sun protection. They found that significantly more participants reported being motivated to improve their sun protection behaviour based on the genetic test result compared to family history information (p-value = $4.01 \times 10^{-4}$) [68].

3.4.2. Evidence for implementing lifestyle changes after a genetic test is mixed and appears to depend on the health condition and type of lifestyle change

Positive lifestyle changes were identified in the literature for people receiving results that suggest they are at high genetic risk of a specific condition compared to those at low genetic risk in relation to:

- Melanoma and age-related macular degeneration: spending less time outdoors during the middle of the day, wearing more protective clothing while outdoors, increasing sunscreen use and undergoing clinical skin examinations [56, 68, 75].
- Thromboembolism: diet, exercise and wearing compression socks/stockings [64];
- Lung cancer: smoking cessation [69].
- Alzheimer's disease and coronary artery disease\(^{10}\): diet, exercise, medications, dietary supplements, stress reduction and mental activities [67].

However, only one of these studies [68] compared the outcomes of participants who received a personalised risk assessment for melanoma based on self-reported family history and genetic test results to assess behavioural changes relating to sun protection. Diseati et al. [68] found that those at higher risk of melanoma (identified from family history assessment, genetic testing or both) were significantly more likely to engage in preventative behaviour to reduce their risk than those with lower risk of melanoma (e.g. reduce sun exposure, increase suncream use, wear protective clothing and examine skin). When exploring the extent of behaviour change by the different types of information, family history alone had the lowest impact on behaviour changes, followed by genetic information. Both family history and genetic information together were most strongly linked to preventative behaviour change.

In contrast to the studies outlined above, in research participants who received genetic test results for a wide range of conditions simultaneously (e.g. via DTC testing) or for specific genetic tests for cardiovascular disease, cancer,\(^{11}\) obesity, arthritis or HCM, there was no evidence for changes in diet or exercise frequency over time [21, 42, 45, 53, 74, 76-78]. Based on the studies included in this review, the evidence for genetic test results having an impact on changes relating to lifestyle factors that are not targeted toward a particular condition, such as diet and exercise, is mixed. The impact on behaviours that are more specific to the condition tested for (e.g. sunscreen use for melanoma) is more consistent. This suggests that the potential for genetic test results to lead to risk-reducing behaviour change should be evaluated individually for each condition and associated behaviour change.

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\(^{10}\) This included those with the genetic variant (APOE $\epsilon4$-positive) demonstrating greater health behaviour changes than those negative for the variant, as well as those aware of an increased risk of both Alzheimer’s disease and coronary artery disease who showed greater changes than those only aware of an increased Alzheimer’s risk.

\(^{11}\) Breast, colorectal, prostate and lung cancer, and melanoma.
3.5. Evidence for engagement with healthcare professionals after receiving genetic test results is limited, and the evidence for uptake of surgical and pharmacological interventions is mixed

Box 4 Summary of REA findings on engagement with healthcare following genetic testing

There were 16 studies included that provided information on whether people change their level of engagement with healthcare professionals following results from genetic tests. Both the motivation to and actual engagement with healthcare professionals after receiving a genetic test were found to be low in the reviewed literature.

Evidence of intending to engage and actual engagement with disease screening/testing, as well as uptake of pharmacological and surgical interventions, was mixed. It appears to depend on the condition being tested for; however, some evidence was mixed across studies for the same condition (e.g. melanoma).

3.5.1. Engagement with healthcare professionals after a genetic test appears to be limited

The studies reviewed suggested limited motivation to engage with healthcare professionals following a genetic test result [45, 53]. However, neither of these two studies used a control group. Actual engagement with healthcare professionals following receipt of genetic test information was also found to be low (i.e. in all studies, only a minority of participants reported engaging with professionals) [45, 53, 63, 65, 68]. One of these studies compared the outcomes of participants who received a personalised risk assessment for melanoma based on self-reported family history and genetic test results. This study, focusing on participants with a high genetic melanoma risk, found that only 14% of participants reported sharing their risk report with a healthcare provider [68].

3.5.2. Mixed evidence was found for the uptake of preventative screening, surgery and medication changes after receiving a genetic test result

Motivation to engage in disease screening or testing was found to be high in participants receiving genetic risk information on breast cancer, melanoma and, as one study showed, on a range of conditions simultaneously12 across samples with and without family history of a genetic condition [42, 54, 60]. However, none of these studies were able to determine whether motivation to engage in screening was greater for people who receive genetic test information compared to those who do not as they did not include control groups. Evidence for engagement with screening/testing in practice, on the other hand, was less consistent. Those who received information on cardiomyopathy risk, melanoma and colorectal cancer (CRC) risk were not significantly more likely to engage with screening [65, 68, 79]. The study by Saya et al. compared

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participants without a strong risk of CRC (based on family history assessment) taking a genetic test for CRC and those who did not take a test (although the group not taking a test was small) and found no significant difference in risk appropriate screening between the two groups. In addition, Diseati, et al. [68] found that of the 14% of participants (100 participants) who shared their risk report for melanoma with a healthcare provider, only 17% of these had additional tests conducted, such as biopsies. In other studies, those who received information on VTE, various types of cancer, melanoma and, for one study, whole genome sequencing (WGS), were substantially more likely to participate in disease screening or testing after receiving genetic test results [64, 66, 76].

Motivation and actual undertaking of surgery was higher for those at greater risk of developing various cancers (including breast, ovarian and gastrointestinal) [54, 80, 81].

Studies of Alzheimer’s disease and coronary artery disease indicate that knowledge of risk can lead to medication changes (e.g. blood pressure and cholesterol medication and fibre supplements) [67, 71]. Studies for other conditions (cardiomyopathy, VTE and one study exploring risk to a variety of conditions) did not identify a link between genetic risk knowledge and medication changes [45, 64, 65].

3.6. Summary and discussion

Overall, the literature suggests that health-related motivations are key reasons why people get genetic testing, although other motivations such as interest in ancestry and a desire to alert offspring and family members of potential risk for health conditions also play a role. With regard to disclosing genetic test results, available evidence indicates that the majority of people report wanting to share test results with healthcare providers, but a smaller proportion actually report sharing this information once tested. There is insufficient evidence to be able to determine how often people share genetic test results with insurers. The evidence around whether genetic tests motivate behaviour change points to the potential for genetic tests to motivate lifestyle change to reduce health risks. However, the evidence around whether genetic tests contribute to actual behaviour change (rather than planned or intended behaviour change) is mixed, as is evidence around whether people engage more with healthcare providers after receiving genetic test results.

Our findings are similarly reflected in by the two systematic reviews that we identified in our literature search. Stewart, et al. [82] reviewed and conducted a meta-analysis on 19 articles exploring the effects of DTC testing on behaviour change (among other things). This review found that one-third of participants reported sharing their DTC test results with a healthcare professional. Participants who paid for a test were more likely to disclose the results to a healthcare professional compared to those who received a free test (25% compared to 1%, respectively). In addition, actual consumers (who paid for a genetic test) were more likely to report the test results to a professional compared to people who received a free genetic test as part of a research study (i.e. not actual consumers) (35% compared to 27%, respectively). Overall, 24% of participants showed any positive lifestyle changes (16% improved diet, 12% improved exercise, 19% of smokers quit smoking and 11% changed supplement use). In addition, 7% of

Breast, colorectal, prostate and lung cancer, and melanoma
participants underwent preventative checks after receiving test results, such as screening and laboratory tests.

Hollands, et al. [83] conducted a systematic review and meta-analyses of 18 studies to explore the impact of communicating genetic risk information on motivation and actual improvements in health behaviours. The authors found no statistically significant impact on health-related behaviour as a result of learning genetic risk information. This was found specifically found in relation to:

- Smoking cessation (for lung or oesophageal cancer and Crohn's disease).
- Reduced alcohol consumption (for cancer and cardiovascular disease).
- Sun protection (for melanoma).
- Diet improvements (for type 2 diabetes, obesity, FH, Alzheimer’s disease, cardiovascular disease and hypertension).
- Improved physical activity (for type 2 diabetes, obesity, FH, Alzheimer’s disease and cardiovascular disease).
- Engagement in screening or behavioural support programme (for type 2 diabetes and CRC).
- Medication use to reduce risk (for Alzheimer’s disease). However, subgroup analysis showed a positive effect on medication use was seen when comparing participants with high and low risk of the disease.
Expert perspectives on current and future developments in predictive genetic testing

In addition to obtaining feedback on the framework from our expert interviewees, we also captured their perspectives on current and future developments in predictive genetic testing. Their reflections broadly fall into four themes: increases in the availability and use of genetic information; insurance considerations when engaging with genetic testing; the relationship between genetic information and health behaviours; and the implications of the increased use of genetic information in future. Each of these themes is discussed in turn below.

The amount of genetic information available and the ability to use it in clinical practice has increased substantially over the past 10 years

Interviewees were asked about key changes over the past decade in their area of expertise as it related to genetic testing. Interviewees noted the key changes to be: (i) an increase in the information available on genetic risk and the number of people who have access to this [INT1, INT2]; (ii) greater capacity to use genetic risk information to determine risk reduction approaches, particularly relating to cancers [INT3]; (iii) greater awareness of concerns regarding inappropriate use of genetic information; and (iv) the need to safeguard against genetic discrimination [INT4]. One interviewee noted that although the term ‘discrimination’ is used with negative connotations, we accept some levels of discernment when it comes to understanding genetic risk (e.g. risk stratification to target treatment), so understanding the context in which information is used is important [INT3]. Another interviewee noted that there is anecdotal evidence of the number of people bringing DTC genetic test results to genetic counsellors has increased, although the absolute numbers are still apparently small [INT1].

Insurance considerations are rarely people’s main concern when engaging with genetic testing

All the interviewees emphasised that insurance considerations are rarely the main motivation for engaging with genetic testing, either clinically or via the DTC market. In the UK, knowledge of family history of a genetic condition and a desire to access support to reduce risk or make reproductive decisions is the primary motivation, rather than making decisions about insurance [INT1, INT3]. This may be partly due to the fact that only a small percentage of people in the UK choose to purchase PMI, due to the availability of medical care via the NHS, and knowledge that this information does not need to be shared with insurers in most cases [INT3]. The main motivations for accessing DTC are less clear but appear to be an interest in ancestry and access to health monitoring information [INT2, INT3, INT5]. Individuals who access DTC tests appear to
be more likely to be interested in health improvement, science and technology than the general population [INT5].

The impact of genetic test results on health behaviour depends on the type of interventions offered

Whether genetic tests results lead to changes to health behaviour depends on both the condition and the behaviour that is targeted for change, according to two interviewees. One interviewee suggested that receiving test results, even those from DTC genetic tests, can increase engagement in surveillance for conditions (e.g. cancer, cardiovascular disease and retinopathies) [INT1]. Another indicated that only about 1% of DTC genetic test consumers make follow-up appointments with medical practitioners as a result of genetic test findings, although this is about what would be expected given likely percentage of healthy individuals who would be at increased risk of the serious genetic conditions included in DTC testing panels [INT5]. However, two interviewees also noted that engagement with interventions depends on whether the benefits of engagement are obvious to the individual and clearly relate to reducing risk of the specific condition in question; genetic test results alone are usually not enough to stimulate behaviour change [INT1, INT3].

In the next five to 10 years, the availability and use of genetic information will increase, but the implications of this for the healthcare system and the insurance industry are unclear

All interviewees thought that over the next five to 10 years, the level of genetic information on health conditions available to individuals will increase, both in terms of the number of conditions for which genetic tests will be available and the number of genetic variants identified. However, their perspectives on the consequences of this for clinical care and the insurance industry varied. One interviewee thought that the use of information on multiple genetic variants would increasingly be used to create PRS for risk-stratifying patients and targeting care, particularly in relation to long-term care needs [INT3]. Another interviewee also highlighted the increasing use of multiple variants, noting that WGS and testing for panels of genes and variants, rather than specific variants within a single gene, could identify ‘incidental findings’, whereby individuals find they are at increased risk of a condition they were not taking a test to investigate [INT4]. For example, someone taking a test for HD could find out they have genetic variants that increase their risk of breast cancer. Unless managed carefully, this will expand problems relating to genetic discrimination and increase the potential for negative impacts on insurers, making it a key influence on genetic testing uptake [INT4].

However, another interviewee felt that the way genetic information is used in clinical settings would not change substantially; a greater range of tests will be available, including improved ability to test for reduced penetrance genes, but use of predictive genetic testing will still be guided by risk (i.e. family history) [INT1]. Similarly, one interviewee was of the view that the potential of predictive genetic testing in the NHS has been overestimated [INT2]. According to this interviewee, while there has been a lot of anticipation regarding the impact of predictive genetic testing on identifying the risk of developing conditions and intervening early, the cases in which such testing performs better than cheaper and less controversial approaches, such as use of family history and environmental risk factors, are rare (e.g. HD) [INT2].
Some participants thought the DTC genetic testing market will benefit from the overall increase in DTC consumer diagnostics and healthcare products, particularly given the availability of at-home blood sample kits that do not use needles, although it will not replace clinical testing [INT5]. However, two other interviewees thought the growth and impact of the DTC market will likely to be limited. One interviewee thought that there will continue to be some growth in terms of number of customers and the amount of information provided by tests, but that this will reach a plateau and the sector will reach saturation [INT2]. The other interviewee thought that the impact of the DTC market will continue to be restricted by the fact that most of the tests offered have very limited, if any, clinical utility [INT3]. This interviewee also highlighted that the impact of genetic testing on the UK insurance industry is very different to the situation in the USA because most preventative care (e.g. breast cancer screening and prophylactic surgery) is not covered by UK insurers; this is provided by the NHS [INT3].
5 Framework for evaluating the risks presented by genetic tests to the UK insurance industry

The framework we have developed is designed to support the assessment of whether a genetic test may be relevant to the UK insurance industry in relation to risk estimation, information asymmetry and potential for anti-selection. It is applicable to predictive or pre-symptomatic genetic testing of adults for a specific condition and does not cover:

• Diagnostic testing in symptomatic individuals.
• Predictions for drug response or personalised treatment for those who have developed a condition.
• WGS and incidental findings.\(^{14}\)

The framework covers four key overarching questions:

1. How useful is a test for characterising the risk of developing a condition? This relates to whether a genetic test provides an individual with clinically meaningful information that could change an insurer’s assessment of that individual’s risk.

2. How many people take the test? This determines the size of the potential risk to insurers if individuals who take genetic tests do not share their results with insurers, linked to question 3.

3. What is the impact of the condition in terms of the length and quality of life of people who develop it? This addresses the effect on insurers of individuals developing the condition, linked to question 4.

4. What is the potential for reducing the risk of developing the condition and managing its effects if it develops? This relates to the financial costs related to treating an individual who has developed a condition (e.g. surgery or other medical interventions), but also the trade-off between these costs and the costs of risk-reducing interventions delivered to individuals to prevent or postpone development of the condition (e.g. lifestyle changes).

How genetic test results may influence an individual’s decision to purchase insurance and whether test results are disclosed to insurers is also important for assessing the risk presented

\(^{14}\) Incidental findings or secondary findings are the identification of genetic variants for a condition that was not the reason for someone obtaining a genetic test. They may arise if a genetic test includes variants in multiple genes or in the results of genomic sequencing that involve the investigation of large stretches of DNA.
by a genetic test. However, as discussed in detail in Section 3, the available evidence in this area is currently too limited to provide clear indications of how people who receive a genetic test result placing them at increased risk of a condition will act with regard to purchasing insurance, particularly in the UK context. Consequently, although this area is important, it is not currently included in the framework.

For each of the four questions included in the current version of the framework, we discuss:

• Factors that contribute to determining the answer to the question.
• How these factors may interact and whether this may increase or decrease the level of risk presented.
• What may influence change in these factors, including change over time.

We present a summary of the framework in Table 3, followed by a detailed explanation of each factor included in the framework in Sections 5.1 to 5.4. We conclude the chapter with an application of the framework to six genetic conditions (Section 5.5).

Table 3 Framework summary

<table>
<thead>
<tr>
<th>Factors relevant to framework area</th>
<th>Description of the factors</th>
<th>Relevance to the framework and the insurance industry</th>
</tr>
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<tbody>
<tr>
<td>How useful is the test for characterising the risk of developing a condition?</td>
<td>Clinical utility</td>
<td>Extent to which clinically relevant action can be taken based on the results of the test. For a test to have clinical utility, it must have demonstrated analytic validity, and scientific and clinical validity.</td>
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<tr>
<td></td>
<td>Alternative information sources</td>
<td>Extent to which predisposition to a given condition can be estimated using information other than genetic test results (e.g. family history or lifestyle).</td>
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<tr>
<td>Factors relevant to framework area</td>
<td>Description of the factors</td>
<td>Relevance to the framework and the insurance industry</td>
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<tr>
<td>How many people take the test?</td>
<td></td>
<td></td>
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<tr>
<td>Societal acceptability</td>
<td>Community's desire for genetic tests, which is influenced by whether the community benefits from the tests, as well as personal preferences and autonomy. Community in this context could be the general population, or those who are already at elevated risk due to family history or other factors.</td>
<td>Interest in genetic testing varies by age, education, knowledge of genetics, family history of genetic conditions and the integration of genetic tests into the healthcare system. Consideration of uptake in certain subgroups may be important for insurers if the subgroup is more likely to have insurance or more likely to be at risk of developing a condition.</td>
</tr>
<tr>
<td>Personal utility</td>
<td>Value of the information to the person being tested.</td>
<td>Personal utility of a genetic test will vary by person and by the characteristics of the condition being tested for. Personal utility of a genetic test is likely to increase as capacity of genetic tests to estimate risk improves and/or as the range and effectiveness of interventions for a condition increase.</td>
</tr>
<tr>
<td>Availability of the test and clinical support for it</td>
<td>How a test is accessed in terms of public (or private) medical system or DTC provision, eligibility criteria and the degree of clinical support both before and after testing.</td>
<td>Under current NHS guidance, most individuals will only be referred for a genetic test if they are suspected by a clinician of having a certain condition, either due to symptoms or family history. Genetic testing for many conditions in the absence of family history or other indicative factors and without interaction with healthcare providers is available via DTC testing. However, most DTC tests that are currently available do not have the same clinical utility as those offered in the NHS.</td>
</tr>
<tr>
<td>Cost of the test</td>
<td>Upfront financial investment undertaken by an individual in purchasing the genetic test.</td>
<td>The impact of test cost on uptake may be limited to tests not currently available via the NHS, and to individuals who do not meet NHS criteria for test access but perceive the personal utility to be high and have the ability to pay. If the technological costs decrease but access to genetic tests via the NHS remains limited to those who meet eligibility criteria, the risk of information asymmetry and associated anti-selection may increase substantially.</td>
</tr>
</tbody>
</table>
Assessing the impact of developments in genetic testing on insurers’ risk exposure

<table>
<thead>
<tr>
<th>Factors relevant to framework area</th>
<th>Description of the factors</th>
<th>Relevance to the framework and the insurance industry</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the impact of the condition in terms of the length and quality of life of people who develop it?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penetrance</td>
<td>Likelihood that specific forms of a gene or genes (genetic variants) will be expressed in an individual and lead to development of the condition.</td>
<td>For a condition to be important for medical underwriting in insurance, it must have high penetrance. Capacity to assess penetrance depends on the type of conditions being tested. For example, for conditions determined by a large number of genes, the likelihood of developing the condition is more challenging to estimate.</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Age range in which the condition being predicted by the genetic test usually occurs.</td>
<td>The age of onset of a condition may affect anti-selection of insurance. For example, an individual at risk of an early onset condition may purchase insurance earlier than they may have otherwise done or, conversely, an individual at risk of a late onset condition may delay seeking insurance. Also, consumers may be able to anti-select if they have reason to believe that they are subject to a late onset condition that has presented no symptoms at the time of purchasing insurance.</td>
</tr>
<tr>
<td>Prognosis and morbidity</td>
<td>Prognosis is the time from development of the condition to death, while morbidity refers to the consequences for quality of life and/or the health of the individual who develops the condition.</td>
<td>Conditions with a high mortality rate (combined with a lack of effective treatment) are important for insurance underwriting, but the time from diagnosis to death and the health state during those years are also important as there may be implications for employment and health and/or social care, which may also have implications for insurance.</td>
</tr>
<tr>
<td>Prevalence</td>
<td>Proportion of people within a population who develop the condition being tested.</td>
<td>Conditions with high prevalence may have a large overall financial impact on insurers. However, conditions with low prevalence may also have an impact if people who are at high genetic risk are disproportionally likely to purchase insurance or make an insurance claim.</td>
</tr>
<tr>
<td>Factors relevant to framework area</td>
<td>Description of the factors</td>
<td>Relevance to the framework and the insurance industry</td>
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<tr>
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<tr>
<td>What is the potential for reducing the risk of developing the condition and managing its effects if it develops?</td>
<td>Risk reduction includes interventions delivered before an individual develops symptoms of a condition or when they have developed early symptoms and prevention may still be possible. Treatment strategies are interventions delivered to people after they have developed a condition, with the aim of reducing its impact on their quality of life and/or life expectancy.</td>
<td>Risk reduction approaches may lead to overdiagnosis and overtreatment, a situation in which an asymptomatic individual is identified as being at high risk of a condition that would not have discernible consequences for them during their lifetime but triggers clinical interventions, which may have an impact on critical illness and medical insurance providers. Conditions for which treatments are available may have implications for medical insurers, while those for which there is no effective treatment present the greatest risk in terms of life insurance.</td>
</tr>
<tr>
<td>Potential for risk reduction and/or treatment</td>
<td>Risk reduction effectiveness is the capacity of a strategy to reduce an individual's risk of developing a condition. Treatment effectiveness is the effect on an individual's prognosis and morbidity. Engagement is the extent to which an individual uses an intervention, which may affect its effectiveness.</td>
<td>The effectiveness of an intervention and the extent to which individuals engage with it are key influences on whether risk reduction or management are feasible for a health condition. Many insurance companies encourage their customers to lead healthy lifestyle and offer financial rewards for doing so (e.g. reduced premiums or discounts on services), but evidence for the impact of risk reduction strategies following genetic tests is mixed and dependent on the condition tested for.</td>
</tr>
<tr>
<td>Effectiveness and engagement</td>
<td>Financial investment required to carry out an intervention.</td>
<td>If an individual is identified as being at genetic risk of a condition, the cost of providing them with risk reduction interventions and treatment if the condition develops will have an impact on the risk a genetic test poses to the insurance industry. This risk will be greatest when the cost of treatment is high, particularly in the absence of preventative interventions.</td>
</tr>
</tbody>
</table>
5.1. How useful is the test for characterising the risk of developing a condition?

The usefulness of a test for characterising an individual’s risk of developing a condition is primarily determined by its clinical utility. However, from an insurance perspective, another key factor influencing usefulness is whether alternative sources of information are available to characterise an individual’s risk, as described below.

5.1.1. Clinical utility

Definitions of clinical utility differ, with some taking a broad approach that encompasses a number of other factors in this framework. This includes personal utility and cost aspects, as well as wider societal factors, such as ethical, legal and social issues, and healthcare organisational processes. Other definitions take a more narrow focus, considering only whether any clinically relevant action can be taken based on the results of the test [84-86]. In this framework, we focus more on the latter definition as we include some of these aspects as separate considerations, and because this is of key relevance to providers of medical insurance. However, we acknowledge that clinically relevant actions may include planning for the onset of conditions for which there is no preventive intervention or treatment.

Demonstration of clinical utility must be preceded by demonstration of analytic validity (i.e. the performance of the laboratory assay used in the genetic test) and scientific and clinical validity (i.e. whether the risk of developing a condition can be sufficiently characterised by interpretation of the information from the laboratory assay) [85]. This is particularly important when considering in considerations of anti-selection risk for life, critical illness and income protection insurance. Assessment of validity also incorporates concepts such as sensitivity, specificity, and absolute and relative risk [15]. Consequently, assessment of test validity is implied when a test is viewed as having sufficient clinical utility to be adopted into clinical practice.

Assessment of the clinical utility of a genetic test is straightforward when limited to tests available via the NHS, as adoption in clinical practice provides the necessary evidence. However, the context in which these tests are viewed as having clinical utility must be considered: in the NHS, most tests are offered to individuals already suspected to be at high risk of a genetic condition due to family history or display of symptoms [INT1, INT3]. Thus, assessment of the clinical utility of a test is more complex when considering access to tests by people who may not be considered eligible to be tested based on NHS criteria (e.g. with no family history of the condition). This is particularly relevant if tests are provided by DTC companies as these may not have the same risk prediction performance (e.g. sensitivity and specificity) as those used by the NHS and cannot be assumed to have similar clinical utility [87-89] [INT1, INT3].

5.1.2. Alternative information sources

For the insurance industry, if the risk of developing a condition can be identified through sources other than a genetic test (e.g. family history or lifestyle factors) that are straightforward to assess, then there should theoretically be no risk of information asymmetry [90]. However, this depends on whether information from a genetic test provides a more accurate estimate of disease risk than these alternatives or can improve risk estimation when combined with them [15, 90, 91].
This will change over time as further genomic research and greater integration of genomics into clinical care lead to improvements in estimation of risk using genetic data. It is likely that in many cases using both genetic test results and other sources of information (particularly family history) will provide better characterisation of individual risk than a genetic test alone [90]. However, this needs to be determined on a test-by-test basis and may differ for conditions where risk is determined based on a small number of genetic variants versus those for which PRS incorporates many genetic variants and data on non-genetic factors [INT1, INT2, INT3].

5.2. How many people take the test?

What proportion of a population take a genetic test, or test uptake, is influenced by societal attitudes towards genetic testing overall and/or use of a specific test, personal utility of test results, cost of the test, and availability and clinical support. Test uptake is a key factor in determining the extent of the impact on the insurance industry; research from Australia suggests that only 2% of the population need to engage with testing for it to result in a significant impact on insurance claims costs [90, 92]. This is particularly relevant for DTC test results, which an individual may choose not to disclose results to their insurance company [15, 90].

5.2.1. Societal acceptability

Societal acceptability of genetic testing, including consideration of subgroups who may be more or less likely to take a test [93], has an impact on both test availability and uptake. It includes wider community desire for the test, which is influenced by whether the community benefits (equally) from providing the tests, as well as personal preferences and autonomy (i.e. an individual is permitted to make their own decision about whether they want to take the test) [15, 93]. Societal acceptability of genetic testing has changed over time [28, 84]; in the last few years WGS has become part of established care within the NHS, driven by government investment in genomic medicine [94, 95] [INT3]. This is likely to impact uptake as interest in genetic testing is linked to whether a test is integrated with the healthcare system [28, 84]. For example, one study in the UK identified that intention to purchase a DTC genetic test was higher when the test results were returned to a doctor [28].

Assessing changes in societal acceptability over time is feasible but potentially challenging as it may differ by the condition tested for and between population subgroups. Interest in genetic testing varies by many factors including age, education, knowledge of genetics and family history of genetic conditions [84, 96]. Consideration of uptake of genetic tests in certain subgroups may be important for insurers if the subgroup is more likely to have insurance (e.g. older age groups) or more likely to be at risk of developing a relevant condition (e.g. those with a family history).

5.2.2. Personal utility

A person's perspective on the personal utility of a test determines uptake at the individual level. Definitions of personal utility differ; broadly speaking, it is considered as 'the value of the information to the person being tested' with a specific reference to the non-clinical impacts of a genetic test, such as sense of control, knowledge and future life/reproductive planning, and motivation to undertake actions that could prevent or allow for early identification of the condition [15, 84, 85, 97-99]. This will necessarily vary between people [84, 85, 99, 100] and also
by the condition being tested for, including whether it can be prevented or treated and the age of onset [98]. It is linked to the clinical utility of a genetic test, as the ‘actionability’ of test results is an important consideration [INT1, INT3] [84, 85, 99, 100]. Assessment of the personal utility of a genetic test is difficult given that it will vary by an individual’s circumstances and preferences, as well as by the characteristics of the condition being tested for. However, as for societal acceptability, the personal utility of a genetic test it likely to increase as capacity to estimate risk improves and/or as the range and effectiveness of interventions for a condition increase, which can be more easily assessed.

5.2.3. Availability and clinical support

In the UK, whether a test is available to individuals via the NHS is a key factor determining uptake. Under current NHS guidance, most individuals will only be referred for a genetic test if they are suspected of having a certain condition, either due to symptoms or family history [101]. Access to genetic tests via clinical routes is therefore determined by a combination of test eligibility [92, 93, 102], the cost-effectiveness of the test and whether this is considered sufficient to justify its use [93, 96, 99, 100, 103, 104], and availability of clinical support for decision making and genetic counselling [93, 99, 105].

Genetic testing for many conditions in the absence of family history or other indicative factors is available privately, particularly via the DTC testing market. Although readily available, the clinical utility and relevance of these tests may not currently be as high as those conducted by clinical genetics or genomic medicine services [INT1, INT3]. Most tests conducted in people without a family history of disease have low predictive value, particularly for polygenic conditions, and a high risk of false positives due to the limitations of the single nucleotide polymorphism (SNP)-
genotyping technology used in DTC testing for detecting rare genetic variants [87-89]. However, these tests present a greater level of risk in that they may not have the same risk prediction performance as those used by the NHS [87-89] and are available without interaction with healthcare providers. Consequently, consumers may receive a less precise risk estimate than they would receive from a clinical test without support for interpreting the significance of results and would not receive a clinical diagnosis if warranted. Although consumers may take DTC results to healthcare providers, in most cases they will only be offered a clinical genetic test if they meet the eligibility guidelines discussed above [INT1]. This could lead to information asymmetry and potentially anti-selection if the DTC results are not disclosed to an insurer or healthcare provider, but the degree of risk is contingent on the performance of the individual DTC test and whether the results still have some clinical utility [15, 90].

The range of conditions for which tests are available, eligibility criteria and preferred route of access (NHS or DTC) is likely to change with the progression of low-cost genome sequencing and the implementation of multifactorial PRS [11]. Monitoring changes in the availability of tests for different conditions should be relatively straightforward given that both NHS and DTC genetic testing services publish this information, although collection of information about specific tests (e.g. variants included and predictive performance of PRS) may not be.
5.2.4. Cost of the test

In the context of this framework, the cost of the test itself is considered as the upfront financial investment undertaken by an individual in purchasing the genetic test [93, 103, 104]. Broader costs are considered above in clinical availability (Section 5.2.3) and below in relation to interventions (Section 5.4.3). Consumer sensitivity to the direct cost of genetic testing has been demonstrated, with studies finding that uptake would increase if a test is free [96]. Some evidence also suggests the public’s willingness to pay for a genetic test may vary by the type of condition tested for, with some correlation between greater willingness to pay and conditions with higher prevalence. Therefore, although assessing change in the cost of genetic tests is relatively straightforward, tracking the impact of price changes on test uptake may be more complex. In the UK, access to genetic testing is free for many conditions via the NHS, but conditional on having a family history of the condition or already experiencing symptoms [2]. Therefore, the impact of test cost on uptake may be limited to tests not currently available via the NHS, and to individuals who do not meet NHS criteria for testing but perceive the personal utility to be high and who have the ability to pay. This will necessarily change if genomic screening becomes more integrated into care provided by the NHS [95], and as the cost of technologies for genetic/genomic testing decreases [106]. If the technological costs decrease but access to genetic tests via the NHS remains limited to those who meet eligibility criteria, the risk of information asymmetry and associated anti-selection may increase substantially.

5.3. What is the impact of the condition in terms of the length and quality of life of people who develop it?

The risk presented by a genetic test to the insurance industry depends on the consequences of the condition tested for in terms of how long an individual will live following development of the condition and the impact it may have on their overall health and quality of life. Assessment of this is informed by the penetrance of the condition, its age of onset, prognosis and morbidity, as well as the prevalence of the condition in the population.

5.3.1. Penetrance

The penetrance is the likelihood that specific forms of a gene or genes (genetic variants) will be expressed in an individual and lead to development of the condition [15, 90, 104, 107]. For a genetic condition to be important for medical underwriting in insurance, it must have high penetrance (i.e. is significantly likely to be expressed in the individual) otherwise it will be challenging to accurately estimate the likelihood of an individual developing a condition, which may have implications for actuarial risk [15]. Capacity to assess penetrance depends on the type of conditions being tested for; for conditions in which risk is determined by a few genes this is relatively straightforward, but for conditions determined by a large number of genes (called polygenic) the likelihood of developing the condition is more challenging to estimate and will change over time as more research is conducted [INT3]. In this context it is not the penetrance of individual variants that is important, but the predictive performance of the PRS that utilises this information to estimate risk of developing a condition.
5.3.2. Age of onset

The age of onset is the age range in which the condition being predicted by the genetic test usually occurs [15, 105, 108, 109]. The age of onset of a condition may affect anti-selection of insurance in a number of ways. For example, an individual who discovers they are at risk of developing an early onset condition may purchase insurance earlier than they may have otherwise [110]. This may raise particular concerns relating to information asymmetry if the individual is asymptomatic and would otherwise be considered low or average risk. Conversely, if an individual is at risk for a late onset condition, they may delay taking out a new insurance policy until they are closer to the age at which the disease may occur, making fewer contributions [108]. However, this may be affected by whether there are preventative interventions available to asymptomatic individuals, and the treatment options for those who develop the condition and how this changes over time [105].

5.3.3. Prognosis and morbidity

The prognosis of a condition is the time from development of the condition to death, while the morbidity of a condition describes the consequences for quality of life and/or the health of the individual who develops the condition [110]. Conditions with a high mortality rate (combined with a lack of effective treatment) are important for insurance underwriting [15], but the time from diagnosis to death, and the health state during those years, are also important as people incur more healthcare costs in their last months of life, regardless of their age [15, 90, 102, 110, 111]. In addition to healthcare costs, morbidity associated with a condition may have implications in terms of lost workdays (or lost housekeeping days), inability to work at all and productivity losses [112], and thus influence critical illness claims. There can also be psychosocial costs associated with a condition that may influence insurance, such as job changes and moving home [112]. Assessment of this will need to be undertaken on a condition-by-condition basis.

5.3.4. Prevalence

The prevalence of a condition in this context refers to the proportion of people within a population who develop the condition being tested for [90, 93, 103, 104, 110]. This relates to the total potential treatment costs in the population related to that condition and thus the potential financial impact on insurers. The importance of the prevalence of a genetic condition in an insurance context is linked to its clinical actionability and prognosis. Conditions with low prevalence may still be relevant from an insurance perspective if a genetic test provides characterisation of disease risk that would not otherwise be available to the individual or the insurer, particularly if the costs associated with treatment are very high and would be covered by an insurer [92], the risk of premature mortality is high or people at risk of the condition are disproportionately likely to purchase insurance. While the prevalence of a condition is straightforward to assess and does not usually vary substantially over time for non-communicable conditions, it does inform the importance of changes in other factors such as uptake (above) or costs and effectiveness of interventions (see Section 5.4).
5.4. What is the potential for reducing the risk of developing the condition and managing its effects if it develops?

If a genetic test indicates an individual is at elevated risk for a condition, the relevance of this to insurers needs to be considered in conjunction with information on potential strategies for reducing or managing that risk, and the type of treatment and support they will need if they develop the condition [92, 100]. Assessment of this requires consideration of the characteristics of available interventions (both risk reduction and treatment related), particularly their effectiveness and their costs, in conjunction with the characteristics of the condition (e.g. age of onset, prognosis and morbidity) discussed above.

5.4.1. Potential for risk reduction and/or treatment

Risk reduction/management strategies refer to interventions delivered before an individual develops symptoms of a condition or when they have developed some early symptoms and prevention may still be possible. Interventions may include increased surveillance or screening behaviours, undertaking surgery, pharmacological therapies and behaviour or lifestyle changes (e.g. nutrition, physical activity, sleep and smoking) [23]. This may have positive implications for some insurers (e.g. life insurance) if this reduces mortality or morbidity risk in individuals who are already insured or enables people to access insurance who would not otherwise be eligible. However, there is also the potential for risk reduction approaches to lead to overdiagnosis and overtreatment, a situation in which an asymptomatic individual is identified as being at elevated risk of a condition that would not have any discernible consequences for them during their lifetime, but triggers clinical interventions such as screening or surgery [113]. This may have implications for the insurance industry, particularly PMI, if overdiagnosis leads to subsequent overuse of interventions that have cost implications (see below).

In contrast, treatment strategies are interventions delivered to people after they have developed a condition, with the aim of reducing its impact on their quality of life and/or life expectancy. However, for some conditions the boundary between risk management and treatment may not be straightforward to define [INT3] and thus we consider all available interventions for a condition together. Assessing the potential for treatment in relation to a specific genetic condition encompasses both whether any interventions have been developed and how accessible they are to the individual [15, 103, 105, 109]. Whether treatments are available via the NHS or private care providers, and whether they are covered by an individual’s PMI, are key determinants of the risk a genetic condition presents to the insurance industry. Genetic tests for conditions for which there is no effective treatment present a greater risk in terms of adverse selection in life insurance, income protection and potentially critical illness cover as in this context the impact of hiding the risk of an untreatable condition is greater than one that can be dealt with [15, 105]. The potential for reducing risk and treating conditions will inevitably develop further over time and although this is condition-specific, monitoring this over time is feasible.

5.4.2. Effectiveness and engagement

The availability of an intervention is not sufficient to ensure its impact on a condition, particularly in relation to risk reduction or management. The effectiveness of the intervention and the extent to which individuals engage with it (e.g. medication compliance or adherence to exercise
regimes) are key determining factors. Risk reduction effectiveness relates to the capacity of a strategy to reduce an individual's risk of developing a condition, while treatment effectiveness refers to the effect on an individual's prognosis and morbidity [93, 103, 105]. However, estimating the impact of risk reduction and treatment strategies is hampered by their application. Evidence for the impact of risk reduction strategies following genetic tests is mixed and dependent on the condition tested for, although many insurance companies now encourage their customers to lead healthier lifestyle and offer financial rewards for doing so (e.g. reduced premiums or discounts on services) [18-23, 90, 91]. In the context of treatment, the 'therapeutic gap' in which the need for treatment for a condition exceeds the ability to treat it can cause challenges [105]. This may be further complicated by the existence of different treatment interventions with different levels of effectiveness, particularly if related to patient subgroups; the issues raised by personalised medicine, including pharmacogenomics, are beyond the scope of this framework.

5.4.3. Intervention costs

If an individual is identified by a genetic test as being at risk of a condition, the cost of providing them with risk reduction interventions, and treatment if the condition develops, will have an impact on the risk a genetic test for that condition poses to the insurance industry. There is a trade-off between risk reduction costs versus treatment costs for a condition that is particularly relevant for PMI. Costs due to greater use of (possibly less expensive) risk reduction measures need to be balanced against reduction of potential long-term costs associated with treatment of the end stages of disease [97]. If cost-effective risk reduction interventions are available, then disclosure of a genetic test result would be beneficial for both the consumer and the insurer and is unlikely to lead to information asymmetry. If the costs of treatment for a condition are high, the risk of information asymmetry is likely to be high, particularly in the absence of preventative interventions.

5.5. Application of the framework to a selection of conditions

In this section, we summarise the available research on the set of exemplar conditions selected in collaboration with ABI:

• Huntington's disease (HD)
• Breast and ovarian cancers
• Familial hypercholesterolaemia (FH)
• Lynch syndrome (LS)
• Coronary heart disease (CHD)
• Frontotemporal dementia (FTD).

These conditions have been selected because they present examples of a range of possible scenarios in terms of:

i. The characteristics of the test.
ii. The characteristics of the conditions.
iii. The availability of interventions to reduce risk of or treat a condition.
iv. Tests/conditions for which factors (e.g. test utility and treatment options) may change over the next five to ten years and thus change perspectives on the potential risk they present.

This process is thus designed to illustrate the importance of different elements of the framework in relation to the potential for information asymmetry and adverse selection, and their implications for risk estimation. It is not designed to determine whether these, or any other tests and conditions, should be considered as being exempt from the current Code.

The process for collating the evidence available for each condition and considering the potential for risk of information asymmetry and adverse selection is outlined in Figure 2. It links the four overarching questions:

1. How useful is a test for characterising the risk of developing a condition?
2. How many people take the test?
3. What is the impact of the condition in terms of the length and quality of life of people who develop it?
4. What is the potential for reducing the risk of developing the condition and managing its effects if it develops?

The diamonds in the figure represent the assessments that need to be made to answer these four questions and are colour coded as purple, light blue, dark blue and green respectively. Determining the outcome of these assessments leads to a path through the framework. The circles represent information that is incorporated into these assessments. The grey rounded rectangles represent starting and ending points for an assessment.

The framework assessment is qualitative, although the framework could be used as the basis for modelling studies in future. Regarding test uptake and penetrance, we considered ‘low’ and ‘high’ based on a percentage scale (i.e. close to 100% uptake or penetrance would be considered ‘high’). For health consequences, we considered the impact in terms of reduction in length and/or quality of life, with substantial lifespan reduction or loss of capacity to live independently considered severe. We considered the prevalence of a condition in the context of the population burden (e.g. hypertension, generally considered a common condition, affects about 1 in 3 people in the UK, while schizophrenia, which is generally considered rare, affects less than 1 in 100 people), although note that the prevalence may be different in the insured population.

In making these assessments, we consider the potential for any risks given the current status quo and also what may change in future. To the extent possible, the most recent data available have been used and we have focused on collecting data on the UK population wherever relevant and feasible. However, for some conditions we could not obtain sufficient data to answer all the framework questions. In particular, it was difficult to obtain information on what the level of uptake for genetic tests would be in either the general population or the insured population of the UK; much of the research focused on uptake in at-risk groups as in the UK most predictive genetic tests are only offered to people identified as being at high risk of developing a condition due to family history or presentation of symptoms.
Figure 2 Framework for assessing the potential risk presented by a genetic test and associated condition to insurers (for detailed explanation see text)
5.5.1. Huntington’s disease

Huntington’s disease (HD) is a neurodegenerative disease caused by a variant in the Huntingtin (HTT) gene. It is incurable and associated with gradual progressive decline in cognitive abilities and motor skills before eventual death. It has been chosen as an example condition for our framework as, under the current Code, it is the only test where individuals have to disclose a genetic test result (for life insurance over £500,000). The data collected for this test and condition are presented in Table 4; the interpretation of these data within the structure of the framework is presented in Figure 3.

**Figure 3 Assessment of genetic test for Huntington’s disease**

HD has the potential to present risks to the insurance industry in relation to life insurance, medical insurance, critical illness cover and income protection insurance. This is because the genetic test has high clinical utility and a moderate engagement with testing by at-risk individuals, the genetic variant has high penetrance, HD’s impacts on morbidity and mortality are severe, and there are no interventions that reduce risk or suppress symptoms. Although genetic tests for HD have no implication for PMI as available interventions are limited and care is provided by the NHS, this may change if novel treatments currently being researched, such as gene therapy, become available for clinical use and are within the remit of PMI. This could also have broader
implications for the insurance industry if it leads to an increase in genetic test uptake among at-risk individuals. Changes to test availability, either through removal of NHS eligibility criteria or provision of DTC or private tests with sufficient clinical utility, would also change the likely risk.

Table 4 Huntington's disease

<table>
<thead>
<tr>
<th>Relevant factors</th>
<th>Research summary</th>
<th>Interpretation</th>
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<tr>
<td><strong>How useful is the test for characterising the risk of developing a condition?</strong></td>
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</tr>
<tr>
<td>Clinical utility</td>
<td>The genetic test for HD has high clinical utility, with analytical sensitivity and specificity of almost 100%, and clinical sensitivity and specificity of nearly 100% [114]. It is also used in the NHS.</td>
<td>The genetic test is useful for characterising the risk of HD. <strong>The genetic test is used in the NHS and is viewed as having high clinical utility.</strong> However, this is based on its use in people who are already likely to be at high risk of developing HD due to family history of the condition or display of early symptoms.</td>
</tr>
<tr>
<td>Alternative information sources</td>
<td>Family history is the only predictor of HD aside from a genetic test: as it is autosomal dominant, if a parent has HD their child has a 50% chance of developing the condition. However, 7–25% of HD cases do not have a known family history of the condition [114].</td>
<td><strong>The genetic test provides additional information</strong> as although family history is the key predictor, not all people with a family history of HD develop the condition.</td>
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<tr>
<td><strong>How many people take the test?</strong></td>
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<tr>
<td>Societal acceptability</td>
<td>Although genetic testing for HD has been available via the NHS for many years, estimates of test uptake among people with a family history are consistently low, both in the UK and abroad. One study estimated that for the at-risk UK population, between 1994 and 2014, uptake was 17.4% (95%CI 16.9–18.0) [115]. This is comparable to another estimate of test uptake in Northern Ireland (12.3–14.6%) [116].</td>
<td><strong>A moderate percentage of at-risk people take the test:</strong> <strong>Currently only around 17% of eligible people engage in testing.</strong> Genetic testing for HD is only available via the NHS and there are eligibility restrictions (relating to family history and/or symptoms). Uptake may be limited by perceived personal utility of the test given the absence of available interventions. <strong>If interventions for HD become available in future, testing uptake may increase.</strong> Currently there is no DTC testing available in the UK.</td>
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15 If a condition is autosomal dominant, only one copy of a gene containing a variant is needed to cause development of a condition.
### Relevant factors

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Personal utility</td>
<td>The personal utility of a predictive genetic test for HD is unclear, as it can enable individuals to plan for the future, especially reproductive decision making, but cannot predict precise age of onset or disease severity [115]. Reasons for low uptake of genetic testing by people at risk for HD may relate to low personal utility: the absence of disease-modifying treatment, financial implications of a positive test result, or perceived stigma around the condition [115]. Future development of interventions to delay onset or reduce the severity of HD symptoms [117] may therefore have an impact on perceived personal utility, which may in turn affect uptake.</td>
<td></td>
</tr>
<tr>
<td>Availability and clinical support</td>
<td>In the UK, testing is only available in the NHS via regional genetic centres and there is no DTC alternative [118]. Genetic counselling is available both prior to and after testing via the NHS.</td>
<td></td>
</tr>
<tr>
<td>Cost of the test</td>
<td>As the test is only available to individuals via the NHS, the cost of the HD genetic test is not currently a consideration for individuals in the UK context. However, HD genetic tests offered in the US often cost several thousand dollars [119].</td>
<td></td>
</tr>
</tbody>
</table>

### What is the impact of the condition in terms of the length and quality of life of people who develop it?

| Penetrance | The penetrance of HD is estimated to be 100% [120] and therefore a positive genetic test result can confirm a diagnosis. However, intermediate length CAG repeat alleles may have reduced penetrance [115]. | The penetrance of the HD variant is high and consequences of HD for morbidity and mortality are severe: People with HD may suffer from depression, dementia, and extrapyramidal and movement disorders, and eventually require full-time care. |
| Age of onset | Typically, symptoms begin at around 30 to 50 years of age [121]. Current tests do not provide a precise estimate of onset age, although recent research suggests that CAG repeat length, in combination with six other genes involved in DNA maintenance, could be used to provide more precise estimates of age of onset in future [122]. | Age of onset is variable, but life expectancy is often substantially reduced. The prevalence of the condition is very low. |
### Prognosis and morbidity

In one study with participants from the UK, Germany, Spain, Italy and France, median survival for an individual with HD was found to be 24 (95%CI 20.8–27.2) years from formal motor diagnosis and 35 (95%CI 29.2–40.8) years from symptom onset [123]. In a recent German study of HD patients, 42.9% suffered from depression, 37.7% dementia, and 30.5% extrapyramidal and movement disorders [124].

### Prevalence

It is very rare condition; incidence in the UK appears to be stable over time and is estimated as 7.2 (95%CI 6.5–7.9) per million person-years [125].

### What is the potential for reducing the risk of developing the condition and managing its effects if it develops?

#### Potential for risk reduction and/or treatment

While there is some evidence to suggest that drug and alcohol abuse can accelerate the age of onset [126, 127], currently, there is no treatment or action that can prevent the disease. Once HD develops, symptoms can be managed via medications, such as antipsychotics and antidepressants; medical aid, such as physical therapy and speech therapy, is also used [124].

Currently there are no risk reduction strategies and no treatments that can reverse the symptoms of HD: Interventions are focused on managing symptoms and providing supportive care.

#### Effectiveness and engagement

Not all individuals who develop HD necessarily engage with available medical treatments, particularly pharmacological therapies. For example, one US study found that 26.4% of HD patients studied did not initiate treatment with tetrabenazine [128].

#### Intervention costs

The estimated the mean annual cost per person of managing HD in the UK is £21,605 [129].

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### 5.5.2. Breast and ovarian cancers

Breast and ovarian cancers are characterised by uncontrolled, abnormal cell growth in the breast and ovarian tissues, which can spread across the body and can result in death. If detected early and preventative actions are taken, the morbidity and mortality associated with the conditions are significantly decreased. These two cancers, and the associated test for *BRCA1/2* gene variants, were selected as example conditions for the framework because they are relatively common cancers, genetic testing is available via the NHS and DTC market, and effective clinical interventions are available. The data collected for this test are presented in Table 5. The interpretation of these data within the framework is presented in Figure 4. The current assessment for *BRCA1/2* testing is in colour. A hypothetical assessment based on changes to key
factors, which would warrant consideration of risk to insurers is shown using uncoloured shapes and dashed lines.

**Figure 4 Assessment of BRCA1/2 genetic test for breast cancer – current assessment in colour; hypothetical future assessment in uncoloured shapes with dashed outlines**

Estimating the risk presented by the currently available BRCA1/2 genetic test for breast and ovarian cancer is made challenging because of a number of factors. BRCA1/2 variants display incomplete penetrance and only account for a small proportion of all breast cancer cases. Consequently, precise estimation of individual risk is not straightforward; some individuals with BRCA1/2 variants will not develop cancer and some individuals who do not carry these variants will develop it due to other causes (some genetic and some environmental). Additionally, multiple interventions exist to reduce the risk of developing breast and ovarian cancer and reduce morbidity and mortality, which are available via the NHS. If genetic characterisation of risk for breast and/or ovarian cancer improves, there may be a risk in relation to PMI, income protection and critical illness cover due to increased medical treatment and potential inability to work during such treatment. As breast cancer appears to occur earlier in those with BRCA1/2 variants, improved age of onset estimation via genetic testing could also be important for insurers.
### Table 5 Breast and ovarian cancers

<table>
<thead>
<tr>
<th>Relevant factors</th>
<th>Research summary</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>How useful is the test for characterising the risk of developing a condition?</td>
<td>The BRCA1/2 predictive genetic test is used in clinical practice in the UK and is considered to have high clinical utility [130, 131]. As there are multiple variants within the BRCA genes, test sensitivity and specificity varies depending on the variants included; a recent international survey of laboratories conducting this test found that the median sensitivity was 99.5% (range 85.2–100%) and specificity of 100% [132]. The potential of PRS for predicting breast and ovarian cancer is currently being investigated, but such tests are not yet available in clinical practice in the UK [46, 133]. The genetic test is useful for characterising the risk of developing breast cancer. <strong>The genetic test used in the NHS and is viewed as having high clinical utility.</strong> However, this is based on its use in people who are already likely to be at high risk of developing breast cancer due to family history of the condition or display of early symptoms. DTC tests available in the UK test for a substantially lower number of variants and the clinical utility is likely to be low. NHS care providers would not make a clinical decision based on these tests; an NHS clinical test would need to be undertaken. <strong>The genetic test provides additional information,</strong> but other non-genetic factors are associated with risk of developing breast cancer. Capacity to predict breast cancer risk is improved by accounting for these factors as well as genetic test results.</td>
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<tr>
<td>Clinical utility</td>
<td></td>
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<tr>
<td>Alternative information sources</td>
<td>While having a first degree female relative with breast or ovarian cancer is a strong predictor for developing the disease, only 10% of breast cancers are hereditary. Lifestyle factors such as reproductive history, radiation therapy, having taken diethylstilbestrol (DES) or hormone therapy, physical inactivity, being overweight and consuming alcohol are all associated with an elevated risk [134]. Recent research suggests that PRS that combined these factors with genetic information may have better performance than those based on genetics alone [135].</td>
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16 Polygenic risk scores could significantly change the insurance and testing landscape, especially as BRCA1/2 variants only account for a minority of breast cancer cases. Yanes et al. recently estimated that ‘those at the highest level of polygenic risk distribution hav[e] a least a twofold increased risk of the disease’ [42].
<table>
<thead>
<tr>
<th>Relevant factors</th>
<th>Research summary</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>How many people take the test?</td>
<td>BRCA testing has been clinically available in the UK since the 1990s, and uptake (in terms of number tested) has increased steadily over time [136]. In a systematic review of uptake rates for breast cancer genetic testing, uptake rates ranged from 25% to 96% (mean 59%) across different population groups and contexts (data from the UK, USA and Canada); personal and family history of breast cancer were the only consistent predictors of uptake [137]. There is evidence that uptake rates are lower in subgroups with lower education, lower income and/or in those with an ethnic minority background [138, 139].</td>
<td><strong>A high percentage of at-risk people take the test:</strong> Around 60% of eligible people engage in genetic testing, although in some instances this may be as high as 96%. In the UK, comprehensive genetic testing for breast cancer is only available via the NHS and there are eligibility restrictions (relating to family history and/or symptoms) on access.</td>
</tr>
<tr>
<td>Societal acceptability</td>
<td>Genetic test results may inform decisions around prophylactic oophorectomy and mastectomy [140]. In this sense, the test has high personal utility. However, there are currently limits to the personal utility of genetic testing for breast and ovarian cancer. Firstly, the penetrance of variants in the BRCA1 and BRCA2 genes is not 100%, so a positive test result is not a guarantee of disease onset [141].</td>
<td></td>
</tr>
<tr>
<td>Personal utility</td>
<td>The BRCA test is available in the NHS for individuals with a family history of cancer or for cascade screening via general practitioner (GP) referral to a specialist genetics clinic [130], which, according to NICE guidance, should be combined with appropriate counselling [142]. Testing of three specific variants of BRCA1/2 are also available with DTC via 23andme [143]</td>
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<tr>
<td>Availability and clinical support</td>
<td>The NHS assumes the cost of the test if offered through the NHS. A DTC BRCA test is available via 23andme’s ‘Health + Ancestry’ test, which is currently £149 [144] and only covers three variants.</td>
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</tr>
<tr>
<td>Relevant factors</td>
<td>Research summary</td>
<td>Interpretation</td>
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<tr>
<td>What is the impact of the condition in terms of the length and quality of life of people who develop it?</td>
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</tbody>
</table>
| Penetrance      | In a meta-analysis of BRCA1 and BRCA2 penetrance, gathering data from patients across Europe, North America, Australia and Hong Kong, Chen et al. estimated that the mean cumulative cancer risks for mutation carriers at age 70 years was 57% for BRCA1 and 49% for BRCA2 mutation carriers for breast cancer, 40% for BRCA1 and 18% for BRCA2 mutation carriers for ovarian cancer [141]. Polygenic risk background can also effect the penetrance of BRCA1/2 [145]. | **The impact of BRCA1/2 variants on morbidity is moderate:** Although age of onset of breast cancer in women with the variants can be earlier, the *prognosis appears to be the same as for breast cancer without an identified genetic cause.*  
**Penetrance of variants vary** from 18% to 57%, depending on gene and cancer, but is generally moderate.  
Overall, it is a moderately common condition. |
<p>| Age of onset    | Individuals with BRCA1 or BRCA2 variants have an earlier age of onset compared to those without these variants [146]. In the UK, the average age of onset is 42 (95%CI 34–56) years for those with BRCA1 variants and 44 (95%CI 35-53) years for those with BRCA2 variants [147]. |                                                                                                                                                                                                             |
| Prognosis and morbidity | In the UK, standardising for age, 95.8% of females survive breast cancer for at least one year and 85% survive breast cancer for five years or more [148], although this depends on the stage of cancer, previous treatment and fitness level [149]. Research, including that undertaken in the UK, suggests that the prognosis of women with BRCA-associated breast cancers appears to be similar to that of women without BRCA1/2 variants [150, 151]. |                                                                                                                                                                                                             |
| Prevalence      | In 2009, NICE estimated the incidence of breast cancer in women to be 148.5 per 100,000 people in the UK [152]. Cancer Research UK estimate that there were 54,700 new cases in 2017 alone [153]. |                                                                                                                                                                                                             |</p>
<table>
<thead>
<tr>
<th>Relevant factors</th>
<th>Research summary</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td><strong>What is the potential for reducing the risk of developing the condition and managing its effects if it develops?</strong></td>
<td>NICE guidance outlines a range of possible risk reduction and treatment strategies following a positive BRCA1/2 test result [142]. This includes behaviour change (alcohol and tobacco use, weight, physical activity), regular screening, risk-reducing surgery (mastectomy or oophorectomy), chemoprevention or use of oral contraceptives. However, the possibility of overdiagnosis and overtreatment of breast cancer has been raised as a concern [154].</td>
<td>There are many risk-reducing interventions available including screening, surgery, chemoprevention and also pharmacological interventions. Preventive interventions are available via the NHS. Treatment following the development of breast or ovarian cancer is covered by the NHS but may also be covered by private insurers.</td>
</tr>
<tr>
<td>Potential for risk reduction and/or treatment</td>
<td>Starting mammography young is of unknown benefit [155] but adherence to risk management strategies is relatively high; one study found an adherence rate of 69% among women with BRCA1/2 variants in the US [156]. Information on genetic susceptibility is less relevant at later ages in the UK as mammography is already widely encouraged for women aged over 50 regardless of genetic testing status, and there is currently no adequate surveillance at all for ovarian cancer [157]. Chemoprevention and oral contraceptives used to reduce the risk of breast and ovarian cancer are associated with an increased risk of other health conditions, which may reduce engagement with these interventions [140, 158, 159].</td>
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<tr>
<td>Effectiveness and engagement</td>
<td>The costs of intervention increase with the advancement of the stage at diagnosis [160]. In England, the average incidence costs per patient are estimated to be roughly between £2,000 and £3,000 per year [161].</td>
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</table>
5.5.3. Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is a condition associated with elevated levels of low-density lipoproteins (LDLs) and a high risk of developing atherosclerosis and CHD. It is caused by variants in the \textit{LDLR}, \textit{ApoB}, \textit{PCSK9} and \textit{LDLRAP1} genes [162]. It is technically a condition that begins in childhood, but as there is no newborn screening for this condition, currently it is not usually detected until adulthood. FH has been selected as an example condition for the framework as it is common and mostly undiagnosed, but there is a genetic test available via the NHS and DTC market. In addition to this, interventions are currently available. The data collected for this test and condition are presented in Table 6. The interpretation of these data within the structure of the framework is presented in Figure 5. The current assessment for FH testing is in colour. A hypothetical assessment based on changes to key factors, which would warrant consideration of risk to insurers is shown using uncoloured shapes and dashed lines.

![Figure 5 Assessment of genetic test for familial hypercholesterolaemia – current assessment in colour; hypothetical future assessment in uncoloured shapes with dashed outlines](image)

The genetic test for FH does not currently present a risk to the UK insurance industry because of the low uptake of this test by at-risk individuals. If uptake becomes high, the characteristics of this condition mean that the risk it presents could increase substantially. However, the genetic variants have high penetrance, the consequences (elevated LDL levels) can be detected from birth and treatment reduces the risk of the major adverse health outcome (CHD) to that of the general
population. Therefore, the risk to insurers may be lessened if access to the genetic test increases over time as planned, such that FH cases are identified in childhood and interventions to reduce LDL levels and consequent CHD risk can be delivered early.

Table 6 Familial hypercholesterolaemia

<table>
<thead>
<tr>
<th>Relevant factors</th>
<th>Research summary</th>
<th>Interpretation</th>
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<tr>
<td><strong>How useful is the test for characterising the risk of developing a condition?</strong></td>
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</table>
| Clinical utility | A next generation sequencing (NGS) test with a 99.99% sensitivity for point mutations for FH is available via the NHS. With regard to the clinical utility of DTC tests, while over 2,900 recognised pathogenic variants have been identified, DTC tests only cover a small number [163]. The clinical utility of polygenic testing for FH is currently unclear, although FH is thought to have a polygenic influence [164]. | The genetic test is not useful for characterising the future risk of developing FH because the condition is present from birth, making the test diagnostic rather than predictive:  
  - The genetic test used in the NHS is viewed as having high clinical utility. However, this is based on its use in people who are already likely to be at high risk of developing FH due to family history of the condition or display of early symptoms.  
  - People with FH have detectable elevated LDL cholesterol levels from birth. The genetic test simply provides confirmation of a clinical diagnosis. |
| Alternative information sources | Other than a genetic test, family history is the only reliable non-clinical indicator of FH. Cholesterol, specifically LDLs, levels can indicate FH, but the genetic origin of high LDL levels can only be confirmed by a genetic test. | |

| **How many people take the test?** | | |
| Societal acceptability | Uptake of FH testing is very low. In one recent US study, which purported to remove ‘barriers of cost, privacy, and access to testing’, uptake of genetic testing was relatively high among confirmed patients [165]. However, it was ‘poor’ among family relatives in cascade screening. The authors cited ‘reluctance to contact family members, fear of genetic discrimination, and fear of knowledge gaps by the identified probands’ as reasons for the low uptake [165, 166]. | A low percentage of at-risk people take the test:  
  - Low uptake is likely to be primarily due to lack of awareness of both high LDL levels and the availability of a test.  
  - The NHS is initiating case finding of people with FH as part of the 2019 NHS Long Term Plan so that treatment can be initiated. This will lead to an increase in test uptake and thus diagnosis and early intervention. |
<table>
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<tr>
<th>Relevant factors</th>
<th>Research summary</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>Personal utility</td>
<td>Taking the FH genetic test could have high personal utility, as those with a positive result may be more likely to remain adherent to prescribed medications (or perhaps make broader lifestyle changes), provide an explanation for why diet and exercise may not have had an impact on LDL level, and can also explain a family history of premature CHD [167]. However, patients may not necessarily understand inconclusive genetic test results [168], as the test may return a variant of uncertain significance, creating uncertainty and limiting its utility [167].</td>
<td></td>
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<tr>
<td>Availability and clinical support</td>
<td>Testing is available via the NHS for those with a clinical diagnosis of FH and cascade testing is available for first-degree relatives of those index cases where a mutation can be identified. It is part of the 2019 NHS Long Term Plan to increase access to the FH test. A DTC company, Randox Health, provides a test for 40 most common genetic mutations that cause FH in the UK across 5 genes, and 23andme tests 24 variants in the LDLR and ApoB genes only [144, 169].</td>
<td></td>
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<tr>
<td>Cost of the test</td>
<td>The test is free via the NHS. With regard to DTC genetic testing, Randox’s FH gene panel test costs £500, while 23andme’s FH test costs £149.</td>
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</table>

**What is the impact of the condition in terms of the length and quality of life of people who develop it?**

| Penetrance                           | Penetration depends on the exact variant and a ‘substantial polygenic contribution might add to the variable penetrance of the disease’ [164]. Current estimates suggest it varies between 73% and 90% [170, 171]. | **The penetrance is relatively high, but health consequences of FH are mild if detected and treated early:**  
• If diagnosed and treated in childhood, life expectancy in people with FH is normal, although there is a potential increase in risk for CHD. |
| Age of onset                          | Patients are born with FH and the disease causes elevated LDL levels from birth [172], but affected men and women have a 30% to 50% chance of having a cardiac event by ages 50 and 60 respectively if the condition is untreated [173]. |                                                                                                   |
### Prognosis and morbidity

If diagnosed and treated early in childhood, individuals with FH can have a normal life expectancy [172]. The main morbidity associated with FH is development of CHD (as described above).

### Prevalence

In the UK, prevalence is estimated to be around 1 in 250, but most cases are undiagnosed; the NHS estimate that fewer than 8% of FH patients have been identified in the UK [174].

<table>
<thead>
<tr>
<th>Relevant factors</th>
<th>Research summary</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>Prognosis and morbidity</td>
<td>If diagnosed and treated early in childhood, individuals with FH can have a normal life expectancy [172]. The main morbidity associated with FH is development of CHD (as described above).</td>
<td></td>
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<tr>
<td>Prevalence</td>
<td>In the UK, prevalence is estimated to be around 1 in 250, but most cases are undiagnosed; the NHS estimate that fewer than 8% of FH patients have been identified in the UK [174].</td>
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</tbody>
</table>

### What is the potential for reducing the risk of developing the condition and managing its effects if it develops?

<table>
<thead>
<tr>
<th>Potential for risk reduction and/or treatment</th>
<th>There is no cure, but to limit the impact of FH on cardiac health, individuals can take much the same steps as for preventing CHD (described in Table 8).</th>
<th>There are <strong>no risk reduction interventions</strong> for FH as it is present from birth, but <strong>effective treatment is available</strong> for the condition.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness and engagement</td>
<td>Unlike for other CHD risk factors, diet and exercise may not be as effective in reducing LDLs. Statins are effective in reducing risk, but their effectiveness is limited by low uptake [175].</td>
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<tr>
<td>Intervention costs</td>
<td>In a 2007 meta-analysis of published data on LDLs, for primary prevention treatment, estimates of statin costs varied between cost per life-year gained (LYG) £8,000 and £30,000 depending on baseline risk [176]. Lifestyle changes to minimise risk have negligible financial costs.</td>
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</table>
5.5.4. Lynch syndrome

Lynch syndrome (LS) is a condition associated with a genetic predisposition to a range of cancers, most notably CRC. Although the genetic test is diagnostic for LS, it is also effectively predictive for CRC. This condition was chosen for the framework as testing is only available via the NHS and family history is a strong predictor of disease onset. The data collected for this test and condition are presented in Table 7. The interpretation of these data within the structure of the framework is presented in Figure 6. The current assessment for LS is shown in colour. A hypothetical assessment based on changes to key factors, which would warrant consideration of risk to insurers is shown using uncoloured shapes and dashed lines.

Figure 6 Assessment of the genetic test for Lynch syndrome – current assessment in colour; hypothetical future assessment in uncoloured shapes with dashed outlines

The risk currently presented by a predictive genetic testing for LS to UK insurers is limited by the low-to-moderate penetrance of the genetic variants included in the test. If characterisation of genetic risk for this condition improves, the elevated risk for development of multiple cancers and associated medical treatment needs may have implications for PMI, income protection and critical illness cover. If genetic testing for LS becomes available via DTC companies or the NHS criteria for testing (currently focused on testing first-degree relatives of people already diagnosed with cancer) changes, the implications for insurers may also change.
### Table 7 Lynch syndrome

<table>
<thead>
<tr>
<th>Relevant factors</th>
<th>Research summary</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td><strong>How useful is the test for characterising the risk of developing a condition?</strong></td>
<td></td>
<td></td>
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<tr>
<td>Clinical utility</td>
<td>A predictive test is currently offered via the NHS for at-risk relatives of patients with a confirmed diagnosis of LS, suggesting high clinical utility [177]. Rahner et al estimate that the test has almost 100% analytical specificity and sensitivity, but with low clinical sensitivity and unknown clinical specificity [178].</td>
<td><strong>The genetic test is useful</strong> for characterising the risk of developing LS:</td>
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<tr>
<td></td>
<td>• The genetic test used in the NHS is viewed as having high clinical utility. However, this is based on its use in people who are already likely to be at high risk of developing LS due to family history of the condition (i.e. cascade screening).</td>
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<td></td>
<td>• The clinical utility for general population screening is unknown (but likely to be low given the prevalence of the condition).</td>
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<tr>
<td></td>
<td>• The genetic test provides additional predictive information, beyond that obtained from family history.</td>
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<tr>
<td>Alternative information sources</td>
<td>Family history is a strong predictor of LS risk, with family members of cases having a 50% risk of the condition [179]. This is the only predictive information source, as other information (namely tumour tissue testing) is diagnostic [177].</td>
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<tr>
<td><strong>How many people take the test?</strong></td>
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<tr>
<td>Societal acceptability</td>
<td>In a 2015 UK study of predictive testing for LS, uptake was 76.7% for first-degree relatives after 12 years of being eligible for testing, but uptake was significantly lower in males and patients under 25 years of age [180]. For those who declined a genetic test, some reasons for refusal included personal decision (38.1%), patient wants to delay testing (4.1%), anxiety/mental health (4.1%) and insurance/financial implications (3.1%) [180].</td>
<td><strong>A high percentage of at-risk people take the test:</strong></td>
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<td></td>
<td>• Over three-quarters of people with a family history engage with testing.</td>
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<td></td>
<td>• The NHS restricts predictive testing to people with a diagnosed first degree relative. No DTC tests are currently available in the UK.</td>
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<tr>
<td>Personal utility</td>
<td>Although LS itself is incurable, a positive test result may motivate behaviour changes that are effective in mitigating risk of CRC [181].</td>
<td></td>
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<tr>
<td>Availability and clinical support</td>
<td>Currently, a predictive test is currently offered via the NHS for at-risk relatives of patients with a confirmed diagnosis of LS (who are offered the test following tumour testing) [182]. 23andme offer testing for a related condition, MUTYH-Associated Polyposis, but not LS [144].</td>
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</tbody>
</table>
### Relevant factors

<table>
<thead>
<tr>
<th>Cost of the test</th>
<th>Research summary</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>It is freely available via the NHS. Currently, no DTC companies offer an LS test.</td>
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</tbody>
</table>

### What is the impact of the condition in terms of the length and quality of life of people who develop it?

<table>
<thead>
<tr>
<th>Penetration</th>
<th>Five genes are primarily associated with LS, and while the penetrance of the variants in these genes varies, overall it is relatively low to moderate, ranging from 0% to 51% for CRC, although this also varies by age and gender [183, 184]. Polygenic risk background can also effect the penetrance of the genes mainly associated with the disease [145].</th>
<th>The penetrance is variable and low-to-moderate, but the health consequences and prevalence are moderate.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- There are different genetic variants that increase risk, and their penetrance is variable, but moderate at most.</td>
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<tr>
<td>- Although mortality is low with early intervention, there are inherent morbidity risks associated with cancer development, including treatment costs following regular screening.</td>
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<tr>
<td>- The prevalence is moderate.</td>
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</tbody>
</table>

| Age of onset | Age of onset for cancers in those who carry relevant genetic variants also varies for 25 to 40 years of age, depending on the specific genetic variant [184, 185]. | |

| Prognosis and morbidity | In LS patients without prior or prevalent cancer at first colonoscopy, ten-year crude survival was 87% after any cancer, 91% if the first cancer was colorectal, 98% if endometrial and 89% if ovarian [184]. However, although mortality is low, given that LS is associated with an elevated risk of several cancers, morbidity and associated costs related to treatment may be significant | |

### Prevalence

| In the UK, it is estimated that around 1 in 300 people have LS [177]. | |

### What is the potential for reducing the risk of developing the condition and managing its effects if it develops?

<p>| Potential for risk reduction and/or treatment | Although LS itself is incurable, a positive test result may motivate behaviour changes that are effective in mitigating risk of CRC [181]. Following a positive test result, patients can undergo early/two-yearly CRC screening with complete colonoscopy from age 25 within the NHS [177, 178]. | Risk-reducing interventions are available via the NHS, such as screening and colonoscopy, but treatment for cancers may have implications for insurers. |</p>
<table>
<thead>
<tr>
<th>Relevant factors</th>
<th>Research summary</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness and engagement</td>
<td>No available data.</td>
<td></td>
</tr>
<tr>
<td>Intervention costs</td>
<td>Positive lifestyle changes have negligible costs to insurers. The NHS covers the cost of colonoscopy, but if accessed privately can cost at least £2,190 per test [186].</td>
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</tr>
</tbody>
</table>

5.5.5. Coronary heart disease

Coronary heart disease (CHD) is a condition that is influenced by many genetic variants and is associated with a build-up of cholesterol in coronary arteries, which in turn results in the heart being deprived of oxygen. If untreated or unprevented, it is fatal and can lead to significant reduction in quality of life. It has been chosen for the framework as it is a common complex polygenic condition for which no clinical genetic testing options are currently available, but research is currently underway to assess the clinical utility of a PRS for the condition. The data collected for this test and condition are presented in Table 8. The interpretation of these data within the structure of the framework is presented in Figure 7. The current assessment for CHD is shown in colour. A hypothetical assessment based on changes to key factors, which would warrant consideration of risk to insurers is shown using uncoloured shapes and dashed lines. Note that penetrance is not included in the framework here as it does not apply to PRS and risk reduction and treatment interventions are grouped together because it is currently unclear how interventions would be targeted based on genetic risk.
The risk presented by predictive genetic testing for CHD is currently limited due to the lack of clinical utility (and thus availability in the NHS) of the test. Tests are offered by DTC providers, but the clinical utility of these is also likely to be low. The predictive performance of a PRS may need to improve before it is considered to have clinical utility as the current predictive performance of PRS being trialled in the NHS is moderate (Harrell C-statistic <0.7) [187]. As PRS for CHD develop, risks may emerge for the UK insurance industry. These risks may be offset given that life expectancy in CHD is not reduced provided appropriate interventions are used, but this depends on uptake and adherence to these interventions.
### Table 8 Coronary heart disease

<table>
<thead>
<tr>
<th>Relevant factors</th>
<th>Research summary</th>
<th>Interpretation</th>
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</table>
| **Clinical utility** | Although not yet widely used in clinical practice, several studies have suggested that PRS could have high clinical utility and effectively stratify risk for CHD, and outperforms other risk class classification tools [187-190].                                                                 | The genetic test is **not currently useful** for characterising the risk of developing CHD:  
  • The test is **not currently used in clinical practice** and its clinical utility is unknown, although it is being trialled for use in the NHS. The clinical utility of a DTC test for CHD is unclear.  
  • **Non-genetic factors can be used to predict CHD** risk; whether it is more effective to use genetic information rather than these factors (or in combination with these factors) is still being determined. |
| **Alternative information sources** | Family history is a strong indicator of premature CHD [191, 192]. Smoking status, cholesterol levels, levels of lipoprotein (a), exercise regularity, diabetes and being obese or overweight also informs CHD risk [193].                                                                 |                                                                                                                                                                                                                                                                                                                                 |

### How many people take the test?

| Societal acceptability | It is hard to estimate the societal acceptability of testing as PRS for CHD is only recently being considered for inclusion into clinical practice. However, in a study of related polygenic cardiac conditions, hypertrophic and dilated cardiomyopathy, 39% of those with relatives at risk undertook genetic testing [194, 195]. | Estimating uptake is challenging because the test is not in common use, but research on other cardiovascular conditions suggests uptake would be moderate.                                                                                                                                                                                                                      |
| Personal utility | As with the societal acceptability of testing, it is hard to estimate personal utility as PRS for CHD is not currently used.                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                 |
| Availability and clinical support | While not widely available in the NHS, a pilot study of polygenic risk scores for CHD will be completed this year in GP check-ups in the north-east of England. The DTC genetic testing company, Invitae, offers an ‘Invitae Cardio Screen’ for over 75 genes [196]. |                                                                                                                                                                                                                                                                                                                                 |
| Cost of the test | In the NHS pilot study, the test is free of charge, while an Invitae Cardio Screen costs USD$250 (~£180).                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                 |

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17 CHD is also widely referred to as ischaemic heart disease or coronary heart disease. We have used the term ‘CHD’ as this is the term most widely used in the NHS.
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<tr>
<th>Relevant factors</th>
<th>Research summary</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td><strong>What is the impact of the condition in terms of the length and quality of life of people who develop it?</strong></td>
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<tr>
<td>Penetrance</td>
<td>Because of its polygenic character, for any one variant associated with the disease penetrance is low; the PRS provides a predicted probability of risk of developing the condition based on aggregating data across genetic variants. The predictive performance is moderate (C-statistic &lt;0.7).</td>
<td>Assuming treatment is effective in those at high genetic risk, life expectancy should not be reduced but there may still be an increase in morbidity, which may present a risk given the high prevalence of the condition.</td>
</tr>
<tr>
<td>Age of onset</td>
<td>CHD can occur at any age, to the extent that early onset coronary heart disease (EOCHD) is occasionally treated as a distinct condition in the literature [197], but the median age of onset in European populations is 63 [198].</td>
<td></td>
</tr>
<tr>
<td>Prognosis and morbidity</td>
<td>With effective treatment, patients with CHD can enjoy a normal life expectancy. However, the costs of CHD morbidity are significant, as one study estimated, 90 million working days were lost because of CHD morbidity [199].</td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>In 2016, prevalence in England was estimated to be around 3% of the adult population [200].</td>
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</table>

| **What is the potential for reducing the risk of developing the condition and managing its effects if it develops?** | | |
| Potential for risk reduction and/or treatment | Several means exist to reduce risk of CHD: eating a diet low in saturated fat, being physically active, smoking cessation, reducing alcohol consumption, minimising blood pressure and taking statins [201]. | Interventions to reduce risk are low cost, effective and provided by the NHS; treatment interventions may be more costly and covered privately. |
| Effectiveness and engagement | All the measures identified above are effective in reducing risk. According to one study, in those over 60, reducing blood pressure reduces the incidence of CHD by about 19% [202]. | |
| Intervention costs | According to Liu et al., ‘Coronary heart disease cost £1.73 billion to the UK health care system in 1999: £2.42 billion in informal care’ [203]. The NHS have stressed that the ‘cost of effective therapy is so low’ and that treatment, such as statins, are ‘inexpensive’. | |
5.5.6. Frontotemporal dementia

Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative condition characterised by early onset behaviour change and executive dysfunction. Approximately 30% of FTD cases occur in people with a family history of FTD or a related condition. Variants in three genes, MAPT, GRN and C9orf72, account for the majority of hereditary FTD, although variants have also been identified in a further 11 genes at very low frequencies. It has been chosen as an example for the framework as it is clinically similar to HD, there is currently no effective cure or treatment and family history can be informative of risk. The data collected for this test and condition are presented in Table 9. The interpretation of these data within the structure of the framework is presented in Figure 8. The current assessment for FTD is shown in colour. A hypothetical assessment based on changes to key factors, which would warrant consideration of risk to insurers, is shown using uncoloured shapes and dashed lines.

**Figure 8 Assessment of the genetic test for frontotemporal dementia – current assessment in colour; hypothetical future assessment in uncoloured shapes with dashed outlines**
Although FTD is similar to HD in terms of overall clinical presentation, prognosis and morbidity, and interventions available, FTD differs from HD in that only about 30% of FTD cases can currently be attributed to a known genetic cause, and there is a comparatively large number of genetic variants that may increase risk and their penetrance is variable. Therefore, predicting if and when someone with these variants will develop FTD is not straightforward. The genetic variability also means that the morbidity and mortality vary substantially between individuals. However, improvements in the characterisation of genetic risk for FTD will increase the potential risks such tests present to the insurance industry.

Table 9 Frontotemporal dementia

<table>
<thead>
<tr>
<th>Relevant factors</th>
<th>Research summary</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>How useful is the test for characterising the risk of developing a condition?</td>
<td></td>
<td>The genetic test is useful for characterising the risk of FTD:</td>
</tr>
<tr>
<td>Clinical utility</td>
<td>Testing for several FTD genes (MAPT, GRN and C9orf72) is available via the NHS, demonstrating clinical utility [204]. Determination of sensitivity and specificity is not straightforward; variants in 11 other genes have been associated with FTD and there may be several genetic modifiers of the condition, so panels of genetic variants are often used in testing and panel make-up varies by supplier [205, 206].</td>
<td>• The genetic test is used in the NHS and is viewed as having high clinical utility. However, this is based on its use in people who are already likely to be at high risk of developing FTD due to family history of the condition or display of early symptoms.</td>
</tr>
<tr>
<td>Alternative information sources</td>
<td>In around 30% of cases, patients have a family history of FTD or a related condition, such as amyotrophic lateral sclerosis; the majority of these cases are autosomal dominant [206]. Changes in grey and white matter may be observed on brain scans at least ten years prior to the onset of symptoms, but the utility of these data for predicting risk of developing the condition is unclear [207].</td>
<td>• Only around 30% of FTD cases have a known genetic basis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• The genetic test provides additional information as although family history is the key predictor, not all people with a family history of FTD develop the condition.</td>
</tr>
<tr>
<td>Relevant factors</td>
<td>Research summary</td>
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| How many people take the test? | Uptake of genetic testing is moderate. Based on data from the UK, Italy, the Netherlands, Sweden and Canada, approximately 70–80% of individuals at risk for FTD do not engage with genetic testing [207]. In the UK, this may be partially attributable to genetic counselling and support systems for FTD being less developed than those in place for other neurodegenerative disorders [207]. | A **moderate percentage of at-risk people take the test:**  
  - In the UK, genetic testing for FTD is available via the NHS with eligibility restrictions (relating to family history and/or symptoms) or via private providers. However, the uptake of FTD testing in the general or insured UK population is unclear.  
  - **Currently only around 20–30% of at-risk people engage in testing,** but uptake may be limited by the limited support available for the condition. **If awareness and support for FTD increase in future, testing uptake may increase.** |
<p>| Societal acceptability | In one study, 13 out of 14 asymptomatic individuals taking the test believed it was beneficial to them. Two persons reported moderate anxiety and one reported moderate depression [208]. Genetic test results may inform reproductive decision making for an individual tested and desire for predictive genetic testing in other family members [206]. However, the outcome of a genetic test for FTD may be inconclusive, identifying a variant of ‘unknown significance’ that may later be reclassified as benign or pathogenic, which may be challenging for recipients to process psychologically [206]. |                                                                                                                                                                                                           |
| Personal utility       | Testing via the NHS is only offered in a predictive context for patients with a confirmed family history and in combination with counselling [206]. The DTC company, Invitae, offers a test for FTD, but it is only available in Canada and the USA. |                                                                                                                                                                                                           |
| Availability and clinical support | The NHS covers the cost of the test, with one FTD test costing £160. It is unclear how much a private test costs, but in one private clinic, an hour consultation alone costs £450 [209]. The Invitae test costs $250 (~£180) in the US and Canada. |                                                                                                                                                                                                           |</p>
<table>
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<tr>
<th>Relevant factors</th>
<th>Research summary</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>What is the impact of the condition in terms of the length and quality of life of people who develop it?</td>
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</table>
| Penetrance | Variants in MAPT are generally fully penetrant, but penetrance is more variable for variants in GRN and C9orf72, appears to be age-related and may be modified by other genetic variants [205, 207, 210]. The C9orf72 variant in particular, a hexanucleotide repeat, presents challenges in terms of unclear pathogenicity of lower repeat numbers, variation in number of repeats within an individual and ambiguity around anticipation [205, 210]. | The penetrance of FTD genetic variants is variable but consequences of FTD for morbidity and mortality are severe:  
- Morbidity of FTD varies depending on the genetic variants involved, but those affected eventually require full-time care.  
- Age of onset is variable and life expectancy may be substantially reduced.  
- The prevalence of FTD is low. |
| Age of onset | Onset may occur any time from adolescence, although average age of onset is 40–60 years [205, 206, 211]. | |
| Prognosis and morbidity | All types of FTD result in a steady decline in function over time, ultimately resulting in complete dependency and need for institutional care [212]. However, prognosis is variable, with survival for some subtypes being only three to five years after symptoms onset and others more than ten years [212]. The clinical characteristics of FTD, and therefore the associated morbidity, vary depending on the genetic variants involved [206]. | |
| Prevalence | In the UK, prevalence of FTD has been estimated to be 10.8 per 100,000 [213]. In the USA, FTD is the second most common form of dementia for those under the age of 65 [214]. | |
| What is the potential for reducing the risk of developing the condition and managing its effects if it develops? | | |
| Potential for risk reduction and/or treatment | Currently, there are no effective curative or prevention options available for FTD, although some pharmacotherapies (e.g. neuroleptic drugs and selective serotonin reuptake inhibitors) may be useful in managing symptoms [207, 212]. Recent research has suggested that active lifestyles are associated with less cognitive decline [215]. Trials are also underway for new therapeutic options for FTD, including gene therapy [206, 207]. | Currently there are no risk reduction strategies and no treatments that can reverse the symptoms of FTD:  
- Interventions are focused on managing symptoms and providing supportive care. |
| Effectiveness and engagement | No data available. | |
In the USA,\textsuperscript{18} the direct annual per patient costs of FTD equalled $47,916 and indirect costs were $71,737 \textsuperscript{[216].}

### 5.5.7. Synthesis of findings from the application of the framework

Assessment of the risk to the insurance industry presented by genetic tests and associated conditions is determined by a complex interplay of factors related to the genetic test itself, engagement with testing, the genetic architecture of the condition, the capacity for reducing risk and the cost of treatment. The example provided by HD is relatively straightforward in that it is caused by a variant in a single gene, everyone who carries the variant develops the condition, and the prognosis and intervention options for HD are clear cut. However, application of the framework to our six example conditions (including HD) demonstrates that this is the exception rather than the rule.

Genetic testing for breast and ovarian cancer (\textit{BRCA1/2}), LS and FTD is limited by currently available knowledge of the genetic variants that increase risk of developing these conditions. For all these conditions, the penetrance of the major genetic variants currently identified was variable and substantially less than 100\%, with the possibility of multiple additional ‘modifier’ genetic variants that impact the penetrance of major variants but are not yet well understood. In practice, this means that not everyone who carries one of the major genetic variants will go on to develop the condition in question. Similarly, not all cases of these conditions are due to a known genetic variant. This makes precise characterisation of individual risk for developing these conditions following a genetic test result challenging.

This may change as developments in genomics lead to a better characterisation of genetic risk for these conditions, or the development of interventions for conditions where treatment options are currently limited (i.e. HD and FTD), particularly if this leads to greater test uptake in some at-risk populations. For one of the conditions we investigated, FH, improvements in genetic testing may actually lead to the condition presenting less of a risk to insurers over time as uptake increases and diagnoses are made in childhood or early adulthood and interventions to reduce risk are applied earlier. Similarly, it is too early to know the impact of a PRS test for CHD on insurers. If this information is used for risk stratification in order to target treatment and reduce CHD risk, similar to the test for FH, then it may prove to be beneficial.

A key consideration for the conditions reviewed, with the exception of CHD, is that the associated genetic tests only used in UK clinical practice for people already suspected as being at elevated risk due to family history or presentation of symptoms. Therefore, because access to these tests is generally limited to people already at elevated risk of developing these conditions, use of these tests by members of the general population is currently low. Although genetic tests for some of

\textsuperscript{18} In the UK, data was only available on dementia more broadly, combining the costs of Alzheimer’s disease and other related neurodegenerative diseases.
these conditions can be accessed via DTC genetic testing companies, the tests offered are not as comprehensive as those offered clinically and their utility will generally be much lower [217]. Any future changes to test access, either due to changes in NHS eligibility or development of DTC offerings, are likely to play a key role in determining whether genetic tests present significant risks to the insurance industry.
6 Summary, reflections and suggestions for future research

We have developed a framework for evaluating the risk of negative impacts on the insurance industry arising from genetic tests, taking into account characteristics of genetic tests as well as behavioural aspects that motivate uptake of genetic tests in the population. This framework is intended to provide a common, transparent approach for evaluating whether a specific condition and associated genetic test presents a potential risk to the insurance industry. In the process of developing and refining the framework, we conducted an REA of the literature on motivations for undergoing genetic testing and how this information may affect engagement with interventions to reduce health risks and insurance-related behaviours. We also interviewed experts to obtain feedback on the framework and explore their perspectives on the potential impact of genetic testing on the UK healthcare and insurance sectors. Finally, we applied the framework to six groups of exemplar conditions to provide insights into different possible scenarios with regard to the type of genetic test, condition and intervention options.

6.1. Findings and reflections

How individuals who receive genetic test results for health conditions use this information plays a key role in the impact of genetic testing on the healthcare sector and the insurance industry. Our REA identified some evidence to suggest that health-related reasons, such as health monitoring or adopting behaviours to treatment to decrease health risks, are important among those who seek out genetic testing, although many also engage in testing due to an interest in ancestry. We also found that while the majority of people who take genetic tests report an intention to share their results with healthcare providers, only a minority do so in practice. The literature on disclosure of genetic test results to insurers and the impact of receiving test results on insurance-related behaviour is limited, and although there is some indication of the potential for information asymmetry and adverse selection, the extent of the issue is unclear. Based on our interviews with experts in the fields of genetic testing and genomics, decisions about purchasing insurance do not appear to be the primary concern when engaging with genetic testing in the UK due to universal healthcare access, relatively low levels of health insurance purchase and implementation of the Code governing the use of these data by insurers.

In terms of the impact of genetic test results on behaviour change, we found that people receiving information that they are at increased genetic risk for developing a condition express motivation to engage in lifestyle changes to reduce this risk. However, the evidence for behaviour change occurring in practice is more mixed and appears to vary depending on the type of health condition
and types of lifestyle changes required to reduce risk. Both motivation to engage with healthcare professionals and actual engagement with healthcare professionals after receiving a genetic test were found to be low, and evidence regarding intended and actual engagement with disease screening, uptake of pharmacological and surgical interventions was mixed.

Applying the framework to the six groups of exemplar conditions highlighted that assessment of the risk to the insurance industry presented by genetic tests and associated conditions is determined by a complex interplay of factors related to the genetic test itself, engagement with testing, the genetic architecture of the condition, the capacity for reducing risk and the cost of treatment.

For some conditions (breast and ovarian cancer, LS and FTD), genetic testing is limited by currently available knowledge of the genetic variants that increase risk of developing these conditions. For all these conditions, the penetrance of the major genetic variants currently identified was variable, which means that not everyone who carries one of the genetic variants will go on to develop the condition in question. Similarly, not all cases of these conditions are due to a known genetic variant. This makes precise characterisation of individual risk for developing these conditions following a genetic test result challenging.

The key factors that may change the risk presented by genetic tests and associated conditions are better characterisation of genetic risk for these conditions or the development of interventions for conditions where treatment options are currently limited (i.e. HD and FTD), particularly if this leads to greater test uptake in some at-risk populations. For some conditions (FH and CHD), if genetic testing improvements are used to target interventions that reduce health risks earlier, this may lead to the condition presenting less of a risk to insurers over time.

With the exception of CHD, the genetic tests investigated are only used in UK clinical practice for people already suspected as being at elevated risk due to family history or presentation of symptoms. Therefore, access to these tests is generally limited to people already at elevated risk of developing these conditions; use of these tests by members of the general population is currently low. Genetic tests for some of these conditions (breast and ovarian cancer, FH and CHD) can be accessed via DTC genetic testing companies regardless of family history. However, the DTC tests currently offered are not as comprehensive as those offered clinically and their utility is generally much lower. Future changes to genetic testing access, either due to changes in NHS eligibility or DTC offerings, will be important in determining whether genetic tests present risks to the insurance industry.

6.2. Potential areas for future research

This research has identified a number of important gaps in the evidence base, most of which could be addressed as part of future research studies and would provide additional insight on the potential impact of genetic testing on the UK insurance industry:

- **Availability of data on genetic tests and conditions.** Making a definitive assessment of the potential risk a genetic condition presents to the insurance industry is complex and limited by the availability of current data from the UK population on test characteristics, availability and update, prognosis and morbidity, and intervention effectiveness and adherence. The advent of clinical polygenic risk scores combined with WGS may make this even more challenging.
Addressing this limitation is beyond the capacity of any individual researcher; it will improve as the field develops and if/when specific tests are incorporated into clinical practice. However, the framework outlined in this document can act as a guide for determining the areas and types of information that warrant monitoring to understand how the risk to insurers may change as research develops further.

- **Lack of research on UK samples.** Research on the impact of genetic test results on insurance-related behaviours and behaviour change is limited, heterogeneous and has many methodological limitations (e.g. sampling from specialised subsections of the population, unstandardised outcome measurements and lack of appropriate comparator groups). Most importantly in a UK context, most research has not been conducted with samples from the UK population, so making inferences about motivations for engaging with genetic testing, how people would use the information and any risk of information asymmetry and adverse selection is difficult. Findings from our expert interviews also indicated that the fundamental differences in healthcare and insurance between the UK and other countries, particularly the US where most research has been conducted, mean that findings from other countries are not easily extrapolated to the UK. Conducting research using UK samples on uptake of and motivations to use genetic tests, and the potential impact of this information on decisions regarding insurance and engagement in risk-reducing behaviours, would be beneficial in addressing this gap.

- **Uncertain likely impact of developments in genetics and genomics on the healthcare and insurance sectors.** The ways in which information about the risk of developing a genetic condition is accessed by individuals and incorporated into clinical practice in the NHS are likely to change over the next five to ten years. While our expert interviewees all agreed that uptake of genetic information and the breadth of information available are both likely to increase, there was less consensus on what the implications of this might be for the healthcare and insurance sectors. How this might affect the risk presented by individual genetic tests to the UK insurance industry is therefore unclear. This uncertainty could be reduced to some extent through research collating the perspectives of key stakeholders (a small amount of which were undertaken for this report) and modelling variation in the elements of the framework outlined here to identify combinations of characteristics of a genetic test, or thresholds these characteristics would need to meet, before a test potentially presents a risk of information asymmetry and adverse selection.
References


Assessing the impact of developments in genetic testing on insurers’ risk exposure


Assessing the impact of developments in genetic testing on insurers’ risk exposure


Assessing the impact of developments in genetic testing on insurers’ risk exposure


“Colonoscopy,” (in en), Fairfield Independent Hospital. As of 08 August 2021: https://www.fairfield.org.uk/treatments/colonoscopy/


Assessing the impact of developments in genetic testing on insurers’ risk exposure


Annex A. Data collection template for the development of the draft framework

<table>
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<th>General information</th>
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<td>• Reviewer initials</td>
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<td>• Authors</td>
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<td>• Include/exclude in the synthesis</td>
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<td>• Objectives of the study</td>
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<th>Overall framework information</th>
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<tbody>
<tr>
<td>• Does the study provide a framework to assess genetic tests?</td>
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<tr>
<td>• Does the study provide a framework to assess/develop policy related to genetic tests?</td>
</tr>
<tr>
<td>• Does the study specifically focus on assessing/developing policy related to the impact of genetic tests on insurance (from insurer or consumer perspectives)?</td>
</tr>
<tr>
<td>• Are specific diseases mentioned? If so, which ones?</td>
</tr>
<tr>
<td>• What is considered with regard to the disease (e.g. prevalence, incidence, morbidity, mortality)?</td>
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</tbody>
</table>
### Information on framework to assess genetic tests

- **Name of the framework (if relevant)**
- **What characteristics does the framework take into account (e.g. analytic validity, clinical validity, clinical utility)?**
- **With regards to analytic validity, what characteristics does the framework consider?**
- **With regards to clinical validity, what characteristics does the framework consider?**
- **With regards to clinical utility, what characteristics does the framework consider?**
- **Does the framework consider availability of alternative diagnosis methods? If so, what information does it take into account?**
- **Does the framework consider availability of treatment for genetic conditions? If so, what information does it take into account?**
- **Does the framework consider potential to reduce risk of developing a genetic condition (medical or lifestyle changes)? If so, what information does it take into account?**
- **Additional information on the framework to assess genetic tests**

### Information on frameworks for assessing policy implications of genetic testing

- **Name of the framework**
- **Country of focus**
- **What characteristics does the framework take into account (e.g. political, economic, legal, ethical or social implications)?**
- **With regards to political factors, what characteristics does the framework consider?**
- **With regards to economic factors, what characteristics does the framework consider (including costs of genetic tests)?**
- **With regards to legal factors, what characteristics does the framework consider?**
- **With regards to ethical factors, what characteristics does the framework consider?**
- **With regards to social factors, what characteristics does the framework consider (e.g. fear of discrimination)?**

### Insurance

- **Does the framework mention the insurance industry specifically?**
- **Does the framework consider insurer concerns (e.g. information asymmetry), consumer concerns (e.g. discrimination, higher premiums) or both?**
- **How are insurer/consumer concerns considered and incorporated?**

### Other

- **Additional information on the framework for assessing policy implications for genetic testing**
- **Other comments**
Annex B. Expert interview protocol

Interview protocol

The Cambridge Centre for Health Services Research (CCHSR), a collaboration between the University of Cambridge and RAND Europe was commissioned by the Association of British Insurers (ABI) to conduct a study to help assess the potential impact of predictive genetic testing on insurers who provide life, health and critical illness protection. This study is designed to inform the next revision of the Code on Genetic Testing and Insurance, an agreement between the UK government and ABI on the use of genetic test results in underwriting insurance policies. As such, it is focused on informing policy development and does not address the commercial implications for any individual insurance company.

As part of this work, the study team has developed a framework for evaluating the impact of genetic tests on the insurance industry through a review of academic and grey literature. In addition, we have conducted a rapid evidence assessment (REA) on individual motivations for testing and behaviours following genetic testing relating to risk reduction and disclosure of genetic test results to insurers and healthcare providers. In order to validate the genetic test evaluation framework and our REA findings, we are conducting a series of interviews with individuals who have expertise relevant to different aspects of genetic testing.

Prior to the interview, we provided you with a consultation document that summarised the aim of the project as well as providing the framework we have developed based on findings from the REA. The interview will be structured around these elements and seeks to ask your opinion on areas related specifically to your area of expertise.

Introduction/general questions

1. Could you briefly describe your professional role and how it relates to genetic testing?
2. What trends have you seen with regards to predictive genetic testing for adult-onset conditions in the last decade?
3. What trends do you anticipate seeing with regards to predictive genetic testing for adult-onset conditions over the next five to ten years?
4. What do you see the impact of genetic testing being for the delivery of care?
Framework specific questions

5. Does the framework capture the key issues of importance when assessing the impact of genetic testing on the insurance industry?

6. In your view, is anything missing or does anything need removing? (Prompt questions based on interviewee expertise):
   
   **Risk of developing a condition**
   
   a. Does the framework consider the right factors (i.e. clinical utility and alternative sources of information) when assessing the usefulness of a test for characterising the risk of developing a condition?

   b. In your view, how important is each factor in characterising the risk of developing a condition? Do you think this weight will change in the next five to ten years? If so, how?

   **Uptake**

   c. Does the framework consider the right factors (i.e. societal acceptability, personal utility, availability and clinical support and cost of the test) as influencing uptake of a test?

   d. In your view, what is the weight of each factor with regards to the uptake of genetic testing? Do you think this weight will change in the next five to ten years? If so, how? What are the main aspects influencing uptake of genetic testing (both enablers and barriers)?

   **Impact of a condition on an individual**

   e. Does the framework consider the right factors (i.e. penetrance, age of onset, prognosis and morbidity, and prevalence) when assessing the impact of a given condition on an individual?

   f. In your view, how important is each factor regards to assessing the impact of a given condition on an individual? Do you think this weight will change in the next five to ten years? If so, how?

   **Risk reduction**

   g. Does the framework consider the right factors (i.e. potential for risk reduction or treatment, effectiveness and engagement, and intervention costs) when assessing the potential for reducing the risk of developing a given condition and managing its effects if it develops?

   h. In your view, how important is each factor with regards to reducing the risk of developing a given condition and managing its effects if it develops? Do you think this weight will change in the next five to ten years? If so, how?

7. Besides the factors that we have just discussed, do you identify any areas for improvement in the framework? (Prompt: clarity, flow, etc.)

8. Considering all the aspects of the framework, what do you think are the main factors that may lead to a change on the impact of genetic testing on the insurance industry in the next five to ten years?
REA-specific questions

9. From your professional experience, what do you think are the main motivations for people seeking predictive genetic testing in the UK?

10. One of the things we are interested in is disclosure of information to healthcare professionals. From your experience, do people who receive predictive genetic test results indicating high risk of developing a condition (not through the NHS) share these results with healthcare professionals?

11. We are also interested in disclosure of information to insurers. However, there is very little information on disclosure of genetic test results to insurers. From your experience, do people who receive predictive genetic test results indicating high risk of developing a condition (not through the NHS) share these results with their insurer?

12. Once people receive results from predictive genetic tests that indicate high risk of developing a condition, do you think they change their level of engagement with healthcare professionals and preventative interventions?

13. People believe that receiving results of increased genetic risk for developing a condition would motivate them to engage in lifestyle changes. However, whether they actually change their behaviour is unclear. From your professional experience and with a focus on the UK context, do people tend to change their lifestyle based on positive results from predictive genetic testing?

   a. If so, do you have evidence on how long they commit to the change and what are the key factors for reverting back to previous lifestyle?
Annex C. Search Strategy for the REA

Box 5 Scopus search string (1)

( TITLE-ABS-KEY ( "genetic test*" OR "genetic risk*" OR "genetic predisposition*" OR "genome wide association stud*" OR "genetic screen*" OR "genomic risk*" OR "genomic knowledge" OR "genetic knowledge" OR "polygenic risk score*" OR "WGS" OR "genome sequenc*" OR "exome sequenc*" OR genotype* OR "personalized genetic*" OR "genetic result*" OR "genomic test*" OR "polygenic score*" OR "polygenic risk*" OR "genome wide score*" ) )
AND
( ( TITLE-ABS-KEY ( insurance OR insurer* OR underwrit* ) W/5 TITLE-ABS-KEY ( "anti-selection" OR "adverse selection" OR disclos* OR claim* OR discriminat* OR obtain OR purchase OR buy OR decision* OR decide OR renew* OR lapse* OR lapsation* OR apply OR application* ) )
OR
( TITLE-ABS (behaviour* OR behavior* OR lifestyle) W/1 TITLE-ABS (change* OR modif*) )
AND
( EXCLUDE ( AFFILCOUNTRY , "China" ) OR EXCLUDE ( AFFILCOUNTRY , "India" ) OR EXCLUDE ( AFFILCOUNTRY , "South Africa" ) OR EXCLUDE ( AFFILCOUNTRY , "Saudi Arabia" ) OR EXCLUDE ( AFFILCOUNTRY , "Russian Federation" ) OR EXCLUDE ( AFFILCOUNTRY , "Iran" ) OR EXCLUDE ( AFFILCOUNTRY , "Malaysia" ) OR EXCLUDE ( AFFILCOUNTRY , "Singapore" ) OR EXCLUDE ( AFFILCOUNTRY , "Thailand" ) OR EXCLUDE ( AFFILCOUNTRY , "Chile" ) OR EXCLUDE ( AFFILCOUNTRY , "Kuwait" ) OR EXCLUDE ( AFFILCOUNTRY , "Colombia" ) OR EXCLUDE ( AFFILCOUNTRY , "Nepal" ) OR EXCLUDE ( AFFILCOUNTRY , "Sri Lanka" ) OR EXCLUDE ( AFFILCOUNTRY , "Argentina" ) OR EXCLUDE ( AFFILCOUNTRY , "Bahrain" ) OR EXCLUDE ( AFFILCOUNTRY , "Bangladesh" ) OR EXCLUDE ( AFFILCOUNTRY , "Botswana" ) OR EXCLUDE ( AFFILCOUNTRY , "Cameroon" ) OR EXCLUDE ( AFFILCOUNTRY , "Congo" ) OR EXCLUDE ( AFFILCOUNTRY , "Democratic Republic Congo" ) OR EXCLUDE ( AFFILCOUNTRY , "Ethiopia" ) OR EXCLUDE ( AFFILCOUNTRY , "Jordan" ) OR EXCLUDE ( AFFILCOUNTRY , "Kenya" ) OR EXCLUDE ( AFFILCOUNTRY , "Malawi" ) OR EXCLUDE ( AFFILCOUNTRY , "Pakistan" ) OR EXCLUDE ( AFFILCOUNTRY , "Qatar" ) OR EXCLUDE ( AFFILCOUNTRY , "Samoa" ) OR EXCLUDE ( AFFILCOUNTRY , "Syrian Arab Republic" ) OR EXCLUDE ( AFFILCOUNTRY , "Tunisia" ) OR EXCLUDE ( AFFILCOUNTRY , "Uganda" ) OR EXCLUDE ( AFFILCOUNTRY , "Uruguay" ) OR EXCLUDE ( AFFILCOUNTRY , "Zambia" ) )
AND
( EXCLUDE ( EXACTKEYWORD , "Nonhuman" ) OR EXCLUDE ( EXACTKEYWORD , "Animals" ) OR EXCLUDE ( EXACTKEYWORD , "Animal" ) OR EXCLUDE ( EXACTKEYWORD , "Animal Experiment" ) OR EXCLUDE ( EXACTKEYWORD , "Mouse" ) OR EXCLUDE ( EXACTKEYWORD , "Mice" ) OR EXCLUDE ( EXACTKEYWORD , "Animal Model" ) OR EXCLUDE ( EXACTKEYWORD , "Behavior, Animal" ) OR EXCLUDE ( EXACTKEYWORD , "Animal Behavior" ) OR EXCLUDE ( EXACTKEYWORD , "Disease Models, Animal" ) OR EXCLUDE ( EXACTKEYWORD , "Animal Tissue" ) OR EXCLUDE ( EXACTKEYWORD , "Mice, Inbred C57BL" ) OR EXCLUDE ( EXACTKEYWORD , "Mice, Knockout" ) )
AND
( EXCLUDE ( AFFILCOUNTRY , "Japan" ) )
Box 6 PsycINFO search string (1)

TI ("genetic test*" OR "genetic risk*" OR "genetic predisposition*" OR "genome wide association stud*" OR "genetic screen*" OR "genomic risk*" OR "genomic knowledge" OR "genetic knowledge" OR "polygenic risk score*" OR "WGS" OR "genome sequenc*" OR "exome sequenc*" OR genotype* OR "personalized genetic*" OR "personalised genetic*" OR "genetic result*" OR "genomic test*" OR "polygenic score*" OR "polygenic risk*" OR "genome wide score*") OR AB ("genetic test*" OR "genetic risk*" OR "genetic predisposition*" OR "genome wide association stud*" OR "genetic screen*" OR "genomic risk*" OR "genomic knowledge" OR "genetic knowledge" OR "polygenic risk score*" OR "WGS" OR "genome sequenc*" OR "exome sequenc*" OR genotype* OR "personalized genetic*" OR "personalised genetic*" OR "genetic result*" OR "genomic test*" OR "polygenic score*" OR "polygenic risk*" OR "genome wide score*") OR KW ("genetic test*" OR "genetic risk*" OR "genetic predisposition*" OR "genome wide association stud*" OR "genomic screen*" OR "genomic risk*" OR "genomic knowledge" OR "genetic knowledge" OR "polygenic risk score*" OR "WGS" OR "genome sequenc*" OR "exome sequenc*" OR genotype* OR "personalized genetic*" OR "personalised genetic*" OR "genetic result*" OR "genomic test*" OR "polygenic score*" OR "polygenic risk*" OR "genome wide score*")

AND

((TI (insurance OR insurer* OR underwrit*) N5 ("anti-selection" OR "adverse selection" OR disclos* OR claim* OR discriminat* OR obtain OR purchase OR buy OR decision* OR decide OR renew* OR lapse* OR lapsation* OR apply OR application*)) OR (AB (insurance OR insurer* OR underwrit*) N5 ("anti-selection" OR "adverse selection" OR disclos* OR claim* OR discriminat* OR obtain OR purchase OR buy OR decision* OR decide OR renew* OR lapse* OR lapsation* OR apply OR application*)) OR (KW (insurance OR insurer* OR underwrit*) N5 ("anti-selection" OR "adverse selection" OR disclos* OR claim* OR discriminat* OR obtain OR purchase OR buy OR decision* OR decide OR renew* OR lapse* OR lapsation* OR apply OR application*)) OR (TI (behaviour* OR behavior* OR lifestyle) N1 (change* OR modif*)) OR (AB (behaviour* OR behavior* OR lifestyle) N1 (change* OR modif*)) OR (KW (behaviour* OR behavior* OR lifestyle) N1 (change* OR modif*))

NOT

Population: animal
Box 7 Scopus search string (2)

( TITLE-ABS-KEY ( "predictive genetic test*" OR "personalized genetic*" OR "personalised genetic*" OR "polygenic score*" OR "polygenic risk*" OR "direct to consumer" OR "direct-to-consumer" ) ) AND ( TITLE-ABS-KEY ( "motivation*" OR "uptake" OR "reason*" ) ) AND NOT ( TITLE-ABS-KEY ( "reproductive*" OR "preimplantation" OR "pre-implantation" OR "IVF" OR "in-vitro" OR "prenatal" OR "newborn" ) )

AND


AND


Box 8 PsycINFO search string (2)

TI ("predictive genetic test*" OR "polygenic risk score*" OR "personalized genetic*" OR "personalised genetic*" OR "polygenic score*" OR "polygenic risk*" OR "direct to consumer" OR "direct-to-consumer") OR AB ("predictive genetic test*" OR "polygenic risk score*" OR "personalized genetic*" OR "personalised genetic*" OR "polygenic score*" OR "polygenic risk*" OR "direct to consumer" OR "direct-to-consumer") OR KW ("predictive genetic test*" OR "polygenic risk score*" OR "personalized genetic*" OR "personalised genetic*" OR "polygenic score*" OR "polygenic risk*" OR "direct to consumer" OR "direct-to-consumer")

NOT

Population: animal
Box 9 Grey literature search string (1)

OpenGrey
"genetic test* AND (insurance OR insurer* OR underwrit* OR "anti-selection" OR "adverse selection" OR disclos*)"
Trip
"predictive genetic test* AND (insurance OR insurer* OR underwrit* OR "anti-selection" OR "adverse selection" OR disclos*)"

Box 10 Grey literature search string (2)

OpenGrey
"genetic test* AND ("motivation" OR "uptake" OR "reason")"
Trip
"predictive genetic test* AND ("motivation" OR "uptake" OR "reason")"
Annex D. Inclusion and exclusion criteria for REA

<table>
<thead>
<tr>
<th>ELEMENT</th>
<th>INCLUSION CRITERIA</th>
<th>EXCLUSION CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publication year</td>
<td>1 January 2015 onwards</td>
<td>2014 and earlier</td>
</tr>
<tr>
<td>Publication</td>
<td>English</td>
<td>Non-English languages</td>
</tr>
<tr>
<td>language</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>Adults (&gt;=18 years) who have not been diagnosed with the disease/condition for</td>
<td>Children (&lt;18 years)</td>
</tr>
<tr>
<td></td>
<td>which they are taking a genetic test (i.e. the test is predictive, not diagnostic)</td>
<td>People who are already have the disease/condition or are assumed to have it</td>
</tr>
<tr>
<td></td>
<td>This does not exclude people with a family history of the condition or other</td>
<td>People who are already have the disease/condition or are assumed to have it</td>
</tr>
<tr>
<td></td>
<td>factors that increase their risk of developing it</td>
<td>(i.e. are displaying symptoms)</td>
</tr>
<tr>
<td></td>
<td>Resident in: UK, USA, Canada, New Zealand, Australia, EU27 countries</td>
<td>Convenience samples of subgroups not directly relevant to the objective (e.g.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>medical students)</td>
</tr>
<tr>
<td>Intervention</td>
<td>Taking a predictive genetic test relating to onset of an adult-onset disease or</td>
<td>Taking a predictive genetic test for a newborn or childhood-onset condition (</td>
</tr>
<tr>
<td></td>
<td>condition (could be real or exploring hypothetical scenario)</td>
<td>including newborn screening programmes)</td>
</tr>
<tr>
<td></td>
<td>Testing within a clinical setting or a DTC test</td>
<td>Taking a test related to pre-implantation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>genetic diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Taking a diagnostic genetic test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Taking a pharmacogenomic test (predictive of drug response, not disease onset)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or tests related to personalised medicine for an existing condition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Receiving results from genetic/genomic research studies</td>
</tr>
</tbody>
</table>
### Comparator

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Similar population that do not take a genetic test and/or receive genetic test results</th>
<th>Individuals who have taken a <em>diagnostic</em> genetic test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self (before/after)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (e.g. qualitative)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Motivations</th>
<th>Motivations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Motivation or reasons for taking a predictive genetic test</td>
<td>Reasons for not taking a predictive genetic test (if this is the only outcome)</td>
</tr>
<tr>
<td></td>
<td>Expectations of the information they will receive from taking a predictive genetic test</td>
<td>Non-health consequences of taking a genetic test (e.g. discrimination)</td>
</tr>
<tr>
<td>Disclosure and insurance</td>
<td>Disclosure and insurance</td>
<td></td>
</tr>
<tr>
<td>Decision on whether to purchase insurance or allow an existing insurance policy to lapse</td>
<td>Disclosure of information to anyone other than insurers or healthcare providers (e.g. family members, partners, employers)</td>
<td></td>
</tr>
<tr>
<td>Disclosure of genetic test results to insurers or healthcare providers</td>
<td>Impact of genetic test information on decision to purchase or not renew travel insurance</td>
<td></td>
</tr>
<tr>
<td>Risk reduction</td>
<td>Current characteristics of insurance provision</td>
<td></td>
</tr>
<tr>
<td>Engagement in activities (including lifestyle, preventive treatment) to reduce risk of a disease/condition, as identified via a predictive genetic test</td>
<td>Information on how to disclose genetic risk information to patients</td>
<td></td>
</tr>
<tr>
<td>Duration for which engagement with risk-reducing activities is sustained</td>
<td>Risk reduction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Association of health-related behaviour, lifestyle factors or other modifiable risks associated with genetic variants or scores</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increase in risk for disease/condition was not identified via a predictive genetic test</td>
<td></td>
</tr>
</tbody>
</table>

### Study design

<table>
<thead>
<tr>
<th>Study design</th>
<th>Systematic reviews (+/- meta-analysis)</th>
<th>Published abstracts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary quantitative empirical studies (case-control or cohort; cross-sectional or longitudinal data collection)</td>
<td>Protocols</td>
</tr>
<tr>
<td></td>
<td>Primary qualitative studies (focus groups or individual interviews)</td>
<td>Clinical practice guidelines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Commentaries and other opinion pieces</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case reports</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Narrative reviews</td>
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<tr>
<td></td>
<td></td>
<td>Rapid evidence assessments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scoping reviews</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reviews for which the contributions of individual studies cannot be identified/disaggregated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reviews for which the search strategy or inclusion/exclusion criteria are not provided</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample characteristics are not explicitly stated (including country of residence and recruitment methods)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marketing material for DTC companies</td>
</tr>
</tbody>
</table>

---

19 Life insurance, private medical insurance or critical illness insurance (these are the three critical types identified by ABI).
Annex E. Data extraction fields for the REA

<table>
<thead>
<tr>
<th>ELEMENT</th>
<th>INFORMATION</th>
</tr>
</thead>
</table>
|Population| • Age range  
| | • Ethnicity  
| | • Country of residence  
| | • Risk status (high-risk group for disease/condition or general population)  
| | • Education level and/or income  
| | • Knowledge of genetics (including through profession) |
|Intervention| • Disease/conditions included in the predictive genetic test  
| | • Whether the test was actually taken or a 'thought experiment' (i.e. hypothetical)  
| | • Setting in which test was taken and results received (i.e. clinical – primary, secondary, genetic counsellor – or DTC, experimental)  
| | • How test results were presented to the recipient (mode of communication, risk communication tools used) |
|Comparator| • Similar population that do not take a genetic test and/or receive genetic test results  
| | • Self (before/after)  
| | • None (e.g. qualitative) |

---

20 This covers situations in which an individual takes a clinical or DTC genetic test as part of a study, as opposed to part of normal clinical practice or through their own initiative. It is not intended to include studies focus on the return of results from genomic studies.
1. Motivations
   • Structured categorisation\(^{21}\)
     i. Encourage adoption of a healthier lifestyle
     ii. Access to information about individual characteristics, including ancestry
     iii. Obtain genetic risk information for family members
     iv. Health monitoring
     v. Assist in financial planning
     vi. Inform decisions about purchasing/retaining insurance coverage
     vii. Other
   • Free text for uncovered options or further elaboration

2. Insurance and disclosure:
   • Whether test results would be disclosed to insurers
   • Whether test results would be disclosed to healthcare providers
   • Whether test results would change behaviour in relation to insurance\(^{22}\) (uptake, lapse, continuation)

3. Risk reduction:
   • Association of health-related behaviour, lifestyle factors or other modifiable risks associated with genetic variants or scores

---

### Study design

- Systematic reviews (+/- meta-analysis)
- Rapid evidence assessment
- Scoping review
- Case/control (cross-sectional or longitudinal)
- Cohort (cross-sectional or longitudinal)
- Focus groups
- Individual interviews

### Study quality

- Strengths of study (qualitative)
- Limitations of study – author defined (qualitative)
- Limitations of the study – researcher defined (qualitative)
- Clarity of population and setting (quantitative)
- Clarity of measurements and definitions of exposures, outcomes and covariates (quantitative)
- Clarity of inclusion/exclusion criteria (quantitative)
- Conflict of interest (qualitative)

---

\(^{21}\) With the exception of (vi) and (vii), based on Cherkas et al. 2010 ‘A survey of UK public interest in Internet-based personal genome testing.’ PLOS One. 5(10):e13473.

\(^{22}\) Collected by type: life insurance, private medical insurance or critical illness insurance (these are the three critical types identified by ABI).
## Annex F. Reviewed studies for the REA

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Publication year</th>
<th>Sample country/ countries of residence</th>
<th>Sampling and recruitment</th>
<th>Sample size</th>
<th>Study type</th>
<th>Condition(s) covered</th>
<th>Intervention(s)</th>
<th>Outcome(s)</th>
<th>Topics covered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayer et al.</td>
<td>2020</td>
<td>Germany</td>
<td>Members of the general public with and without obesity</td>
<td>1357</td>
<td>No comparator</td>
<td>NA</td>
<td>Hypothetical genetic test</td>
<td>Motivation to take test, Changes to diet</td>
<td>✓  ✓  ✓</td>
</tr>
<tr>
<td>Bonner et al.</td>
<td>2018</td>
<td>Australia</td>
<td>First-degree at-risk relatives of a person with HCM</td>
<td>32</td>
<td>No comparator</td>
<td>HCM</td>
<td>Real-world genetic test</td>
<td>Motivation to take test, Disclosure to insurers, Lifestyle changes</td>
<td>✓  ✓  ✓</td>
</tr>
<tr>
<td>Celis-Morales et al.</td>
<td>2016</td>
<td>Ireland, The Netherlands, Spain, Greece, the UK, Poland and Germany</td>
<td>Adults from the general population</td>
<td>1269 (completed the study)</td>
<td>No comparator</td>
<td>NA</td>
<td>Genetic test taken for study – compared those with test to those with non-personalised health information</td>
<td>Lifestyle changes</td>
<td>✓</td>
</tr>
<tr>
<td>Christensen et al.</td>
<td>2015</td>
<td>USA</td>
<td>Secondary analysis of data from the REVEAL study (which enrolled participants with or without a first degree relative with Alzheimer’s)</td>
<td>249 (actively recruited to the study) 546 (self-referred)</td>
<td>Comparator – longitudinal (6 weeks and 12 months)</td>
<td>Alzheimer’s disease</td>
<td>Genetic test taken for study-comparing participants who were actively recruited and self-referred to study</td>
<td>Changes to insurance, Lifestyle changes, Medication changes</td>
<td>✓  ✓</td>
</tr>
<tr>
<td>Study reference</td>
<td>Publication year</td>
<td>Sample country/countries of residence</td>
<td>Sampling and recruitment</td>
<td>Sample size</td>
<td>Study type</td>
<td>Condition(s) covered</td>
<td>Intervention(s)</td>
<td>Outcome(s)</td>
<td>Topics covered</td>
</tr>
<tr>
<td>----------------</td>
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</tr>
<tr>
<td>Christensen et al.</td>
<td>2016</td>
<td>USA</td>
<td>Cognitively normal adults (most with first degree relative with Alzheimer’s disease)</td>
<td>119 (AD and CAD) 138 (AD only)</td>
<td>Comparator – longitudinal (6 weeks, 6 months and 12 months)</td>
<td>Alzheimer’s disease and coronary artery disease</td>
<td>Genetic test taken for study – compare those informed only about Alzheimer’s disease and those with Alzheimer’s disease and coronary artery disease, also split by results given in-person and by phone.</td>
<td>Disclosure to healthcare professional Lifestyle changes</td>
<td></td>
</tr>
<tr>
<td>Dalpé et al.</td>
<td>2017</td>
<td>Canada</td>
<td>Women 35–55 who have not been diagnosed with breast cancer</td>
<td>Survey: 36 Interviews: 14</td>
<td>No comparator</td>
<td>Breast cancer</td>
<td>Hypothetical genetic test</td>
<td>Disclosure to insurers Changes to insurance</td>
<td>✓</td>
</tr>
<tr>
<td>Diseati et al.</td>
<td>2015</td>
<td>USA</td>
<td>Participants of CPMC study without a diagnosis of melanoma</td>
<td>718</td>
<td>No comparator</td>
<td>Melanoma</td>
<td>Genetic test taken for study</td>
<td>Disclosure to HCP Lifestyle changes</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Dong et al.</td>
<td>2019</td>
<td>USA</td>
<td>College students</td>
<td>288</td>
<td>No comparator</td>
<td>Obesity</td>
<td>Hypothetical genetic test</td>
<td>Motivations to take test</td>
<td>✓</td>
</tr>
<tr>
<td>Elson et al.</td>
<td>2019</td>
<td>USA</td>
<td>Customers of 23andMe aged over 30</td>
<td>1244 (positive for the genetic variant) 1110 (negative)</td>
<td>Comparator – cross-sectional</td>
<td>VTE</td>
<td>Real-world genetic test</td>
<td>Disclosure to HCP Lifestyle changes Uptake of screening Changes to medication</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Study reference</td>
<td>Publication year</td>
<td>Sample country/countries of residence</td>
<td>Sampling and recruitment</td>
<td>Sample size</td>
<td>Study type</td>
<td>Condition(s) covered</td>
<td>Intervention(s)</td>
<td>Outcome(s)</td>
<td>Topics covered</td>
</tr>
<tr>
<td>----------------</td>
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</tr>
<tr>
<td>Fenton et al.</td>
<td>2019</td>
<td>Australia</td>
<td>Recruited from the sample of another study from a cancer research database, aged 18–69, no history of melanoma</td>
<td>30</td>
<td>No comparator</td>
<td>Melanoma</td>
<td>Genetic test taken for study</td>
<td>Lifestyle changes</td>
<td>✓</td>
</tr>
<tr>
<td>Flores et al.</td>
<td>2016</td>
<td>USA</td>
<td>Sisters or daughters of female breast cancer patients enrolled in the REACH trial</td>
<td>149</td>
<td>No comparator</td>
<td>Breast cancer</td>
<td>Hypothetical genetic test</td>
<td>Motivation to take test</td>
<td>✓</td>
</tr>
<tr>
<td>Frost et al.</td>
<td>2019</td>
<td>USA, Canada and Australia</td>
<td>Random sample of women enrolled in the Breast Cancer Family Registry aged 30–65</td>
<td>32</td>
<td>No comparator</td>
<td>Breast cancer</td>
<td>Hypothetical genetic test</td>
<td>Motivation to take test</td>
<td>✓, ✓</td>
</tr>
<tr>
<td>Gray et al.</td>
<td>2016</td>
<td>USA</td>
<td>New customers of 23andMe28 and Pathway Genomics who had not been tested before and no history of cancer</td>
<td>762 with complete data</td>
<td>No comparator</td>
<td>Breast, colorectal, prostate and lung cancer, and melanoma</td>
<td>Real-world genetic test</td>
<td>Lifestyle changes</td>
<td>✓</td>
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<tr>
<td>Hartz et al.</td>
<td>2015</td>
<td>USA</td>
<td>Nicotine-dependent participants of the Collaborative Genetic Study of Nicotine Dependence study</td>
<td>50</td>
<td>No comparator</td>
<td>Lung cancer, breast or prostate cancer, colorectal cancer, heart attack and type 2 diabetes</td>
<td>Genetic test taken for study</td>
<td>Disclosure to HCP</td>
<td>✓, ✓</td>
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<tr>
<td>Howe at al.</td>
<td>2015</td>
<td>USA</td>
<td>Women aged 30-60 with a family history of breast cancer</td>
<td>478</td>
<td>No comparator</td>
<td>Breast cancer</td>
<td>Hypothetical genetic test</td>
<td>Motivation to take test</td>
<td>✓, ✓, ✓</td>
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<tr>
<td>Study reference</td>
<td>Publication year</td>
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<tr>
<td>Koeller et al.</td>
<td>2017</td>
<td>USA</td>
<td>Participants who purchased a DTC test through 23andMe, members of PatientsLikeMe (Pathway Genomics) and visitors to the Genomic Pathways website were invited.</td>
<td>43 (sought genetic counselling) 983 (did not seek counselling)</td>
<td>Comparator – longitudinal (before results, two weeks after results and six months after)</td>
<td>NA</td>
<td>Real world genetic test</td>
<td>Motivation to take test Disclosure to HCP Lifestyle changes</td>
<td>✓</td>
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<tr>
<td>Marsaux et al.</td>
<td>2016</td>
<td>Germany, Greece, Ireland, the Netherlands, Poland, Spain, and the UK</td>
<td>Participants of the Food4Me study, aged 18+ with no medically required nutritional requirements</td>
<td>874 (FTO risk status) 405 (FTO non-risk status)</td>
<td>Comparator – longitudinal (day of test, three months, six months)</td>
<td>Obesity</td>
<td>Genetic test taken for study</td>
<td>Lifestyle changes</td>
<td>✓</td>
</tr>
<tr>
<td>Mavroidopoulou et al.</td>
<td>2015</td>
<td>Greece</td>
<td>Students from various disciplines</td>
<td>725</td>
<td>No comparator</td>
<td>NA</td>
<td>Hypothetical genetic test</td>
<td>Motivation to take test Disclosure to HCP Lifestyle changes</td>
<td>✓</td>
</tr>
<tr>
<td>McCarty et al.</td>
<td>2018</td>
<td>USA</td>
<td>Patients aged 50–65 registered at an optometrist with a family history of age-related macular degeneration</td>
<td>101</td>
<td>No comparator</td>
<td>Age-related macular degeneration</td>
<td>Genetic test taken for study</td>
<td>Motivation to take test Disclosure to HCP Lifestyle changes</td>
<td>✓</td>
</tr>
<tr>
<td>McGarragle et al.</td>
<td>2020</td>
<td>Canada</td>
<td>Patients in the Familial Gastrointestinal Cancer Registry with confirmed or likely CDH1 variants and had been recommended to undergo prophylactic total gastrectomy</td>
<td>24</td>
<td>No comparator</td>
<td>Hereditary diffuse gastric cancer</td>
<td>Unknown</td>
<td>Surgery uptake</td>
<td></td>
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<tr>
<td>Study reference</td>
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<td>Intervention(s)</td>
<td>Outcome(s)</td>
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<tr>
<td>Meisel et al.</td>
<td>2017</td>
<td>UK</td>
<td>Women contacted during the UK ONS’ monthly survey aged 18–74</td>
<td>837</td>
<td>No comparator</td>
<td>Breast and ovarian cancer</td>
<td>Hypothetical genetic test</td>
<td>Lifestyle change</td>
<td></td>
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<tr>
<td>Meiser et al.</td>
<td>2020</td>
<td>Australia</td>
<td>Carrier of a pathogenic cancer variant whose file had been included in the audit</td>
<td>215</td>
<td>No comparator</td>
<td>Hereditary cancers</td>
<td>Real-world genetic test</td>
<td>Surgery uptake</td>
<td></td>
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<tr>
<td>Metcalfe et al.</td>
<td>2018</td>
<td>Australia</td>
<td>Non-expert members of the public</td>
<td>56</td>
<td>No comparator</td>
<td>NA</td>
<td>Hypothetical genetic test</td>
<td>Motivation to take test</td>
<td></td>
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<tr>
<td>Miller et al.</td>
<td>2019</td>
<td>USA</td>
<td>Participants of the ClinSeq study with VUS in 1 of 20 cardiomyopathy-associated genes</td>
<td>68</td>
<td>No comparator</td>
<td>Cardiomyopathy</td>
<td>Genetic test taken for study</td>
<td>Disclosure to HCP, Lifestyle changes, Screening uptake, Medication changes</td>
<td></td>
</tr>
<tr>
<td>Oliveri et al.</td>
<td>2020</td>
<td>Italy</td>
<td>Customers of a GenomeLab test</td>
<td>152</td>
<td>No comparator</td>
<td>Nutrigenomics, thrombophilia, BRCA, celiac disease, cancer, HD, hemochromatosis, Fragile X, fibrosis, Alzheimer’s disease</td>
<td>Real-world genetic test</td>
<td>Motivation to take test, Disclosure to HCP, Lifestyle changes, Screening uptake</td>
<td></td>
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<tr>
<td>Roberts et al.</td>
<td>2017</td>
<td>USA</td>
<td>New customers of 23andMe and Pathway Genomics with complete data</td>
<td>1042</td>
<td>No comparator</td>
<td>Range of (unspecified) conditions</td>
<td>Real-world genetic test</td>
<td>Motivation to take test, Lifestyle changes</td>
<td></td>
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<tr>
<td>Roke et al.</td>
<td>2017</td>
<td>Canada</td>
<td>Women aged 18–25 with regular menstrual cycles who did not take omega 3 supplements or eat fish more than twice a week</td>
<td>28 (genetic group), 29 (non-genetic group)</td>
<td>Comparator – longitudinal (unknown time point and 12 weeks)</td>
<td>Omega-3 intake requirements</td>
<td>Genetic test taken for study</td>
<td>Lifestyle changes</td>
<td></td>
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</tbody>
</table>

Topics covered:
- Motivation
- Disclosure
- Behaviour

✓ denotes presence; blank denotes absence.
<table>
<thead>
<tr>
<th>Study reference</th>
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<th>Topics covered</th>
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<tbody>
<tr>
<td>Savard et al.</td>
<td>2020</td>
<td>Australia</td>
<td>Members of the public (focus groups) and participants of a wider study who’d had a genetic test (survey)</td>
<td>56 in focus groups 40 in interviews</td>
<td>No comparator</td>
<td>Serious preventable and non-preventable conditions</td>
<td>Real–world genetic test (survey participants) Hypothetical genetic test (interviewees)</td>
<td>Lifestyle changes</td>
<td>✓</td>
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<tr>
<td>Saya et al.</td>
<td>2020</td>
<td>Australia</td>
<td>Patients from four Australian general practice aged 45–74 with little-no history of colorectal cancer</td>
<td>150 (126 took test)</td>
<td>No comparator</td>
<td>Colorectal cancer</td>
<td>Genetic test taken for study (for 126 participants)</td>
<td>Screening uptake</td>
<td>✓</td>
</tr>
<tr>
<td>Schiffman et al.</td>
<td>2016</td>
<td>USA</td>
<td>Psychology students from 1 college</td>
<td>83</td>
<td>No comparator</td>
<td>Schizophrenia</td>
<td>Hypothetical genetic test</td>
<td>Motivation to take test Lifestyle changes</td>
<td>✓ ✓</td>
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<tr>
<td>Shefer et al.</td>
<td>2016</td>
<td>England</td>
<td>Participants of the INFORM trial (blood donors with no history of CVD aged 40–84)</td>
<td>41 (interviews) 13 (focus groups)</td>
<td>No comparator</td>
<td>Coronary heart disease</td>
<td>Genetic test taken for study</td>
<td>Lifestyle changes</td>
<td>✓</td>
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<tr>
<td>Smit et al.</td>
<td>2017</td>
<td>Australia</td>
<td>Participants without a personal history of melanoma, recruited from the Cancer Council New South Wales</td>
<td>103 (survey) 30 (interview)</td>
<td>No comparator</td>
<td>Melanoma</td>
<td>Genetic test taken for study Disclosure to HCP Screening uptake</td>
<td>✓ ✓</td>
<td></td>
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<tr>
<td>Smit et al.</td>
<td>2015</td>
<td>Australia</td>
<td>Recruited via the ‘Join a Research Study’ database, aged 18+ and no personal history of melanoma</td>
<td>34</td>
<td>No comparator</td>
<td>Melanoma</td>
<td>Hypothetical genetic test</td>
<td>Motivation to take test Insurance impact Lifestyle changes Screening uptake</td>
<td>✓ ✓ ✓</td>
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<tr>
<td>Snell et al.</td>
<td>2020</td>
<td>Finland</td>
<td>Participants of the GeneRISK project</td>
<td>40</td>
<td>No comparator</td>
<td>Cardiovascular risk</td>
<td>Genetic test taken for study</td>
<td>Motivation to take test Lifestyle changes Engagement with HCP</td>
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<tr>
<td>Surampalli et al.</td>
<td>2015</td>
<td>USA</td>
<td>Participants of the gene discovery study with a 50% risk of inheriting VCP disease</td>
<td>20 (with complete data)</td>
<td>No comparator</td>
<td>VCP inclusion body myopathy, Paget disease of bone and frontotemporal dementia</td>
<td>Genetic test taken for study</td>
<td>Motivation to take test Lifestyle changes</td>
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<tr>
<td>Taber et al.</td>
<td>2015</td>
<td>USA</td>
<td>Participants of the ClinSeq study (aged 45–65 regarding heart disease)</td>
<td>469</td>
<td>No comparator</td>
<td>Heart disease</td>
<td>Genetic test taken for study</td>
<td>Motivation to take test Lifestyle changes</td>
<td></td>
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<tr>
<td>Van Der Wouden et al.</td>
<td>2016</td>
<td>USA</td>
<td>New customers to 23andMe and Pathway Genomics</td>
<td>Discussed results with PCP: 278 Discussed results with other HCP only: 78 Did not discuss results with any HCP: 670</td>
<td>Comparator – longitudinal (two weeks and six months)</td>
<td>Range of (unspecified) conditions</td>
<td>Real–world genetic test</td>
<td>Motivation to take test Disclosure to HCP</td>
<td></td>
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<tr>
<td>Waltz et al.</td>
<td>2018</td>
<td>USA</td>
<td>Participants of the GeneScreen study, aged 23–84</td>
<td>50</td>
<td>No comparator</td>
<td>11 rare conditions for which treatment and/or prevention options are available</td>
<td>Genetic test taken for study</td>
<td>Motivation to take test</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Motivation</th>
<th>Disclosure</th>
<th>Behaviour</th>
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<tr>
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<td>Wöhlke et al.</td>
<td>2020</td>
<td>Italy and Germany</td>
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<tr>
<td>Yanes et al.</td>
<td>2020</td>
<td>Australia</td>
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<tr>
<td>Zallen et al.</td>
<td>2018</td>
<td>USA</td>
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<tr>
<td>Zoltick et al.</td>
<td>2019</td>
<td>USA</td>
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