UK CANCER GENETICS GROUP

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Prenatal diagnosis and pre-implantation genetic testing for germline cancer susceptibility gene variants

Guidance for clinical practice

April 2023

Produced by the Cancer Genetics Group and Fetal Genomics Group for the British Society for Genetic Medicine

About this report

This guidance covers accessibility to reproductive choices for individuals and couples with a germline cancer susceptibility gene variant (gCSGV). It was produced by the Cancer Genetics Group (CGG) and the Fetal Genomics Group (FGG) for the British Society for Genetic Medicine.

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Introduction

This guideline covers accessibility to reproductive choices for individuals and couples with a germline cancer susceptibility gene variant (gCSGV). Individuals and couples have the right to be involved in discussions and make informed decisions about their care.[1] There is currently a lack of national consensus guidance in the UK, governing the use of prenatal diagnosis (PND) and pre-implantation genetic testing for monogenic disorders (PGT-M) for gCSGVs. This lack of consensus has led to considerable disparities in care across the UK, and inequitable access to reproductive options for families living with cancer susceptibility syndromes.

Who are these guidelines for?

- Healthcare professionals (HCPs)
- Individuals and couples with a gCSGV and their families
- Policy makers and charities supporting people with cancer susceptibility syndromes

Executive summary

- PND and PGT-M should be discussed as standard with all individuals/couples who are at risk of having a child with a cancer susceptibility syndrome to ensure they are aware of all their reproductive options and can make an informed decision about which option is best for them. Children at risk of a cancer susceptibility condition should be advised to seek referral in adulthood, if they wish, when they are thinking about predictive testing or planning a family, in order to discuss the reproductive options available to them.
- There should be a secure and contemporaneous record of the discussions with individuals/couples relating to reproductive options during the predictive or diagnostic genetic testing process, by an appropriately trained genetic/genomic HCP, for all gCSGVs whether of moderate or high penetrance.
- For the purposes of this document, the conditions listed in Appendix 3 of this guidance document have been taken from the National Genomic Test Directory and are considered to be well-characterised conditions with high cancer penetrance.
- Counselling regarding prenatal options for moderate risk gCSGVs and sex-specific variable penetrance gCSGVs should be provided by appropriately trained genetic/genomic HCPs with expertise in this area. Information should be available and presented without bias. Although HCPs and lay group members are of the opinion that only a minority of individuals/couples with a gCSGV would consider PND or PGT-M, careful and sensitive genetic counselling regarding these reproductive options should be offered.
- PND should be completed within the first or early second trimester to enable individuals/couples who decide to end the pregnancy to do so before 24 weeks' gestation under the Abortion Act[i] using form HSA1 and citing Ground C.
- Multidisciplinary team discussion is essential for moderate penetrance and sex-specific variable penetrance gCSGVs and in any situation where the HCP has concerns about the understanding of the individual/couple with regard to their options or where the HCP feels conflicted due to their personal views.
- This guidance should be reviewed in 2 years.

[i] Applications for abortion should use Certificate A form HSA1 citing Ground C ('the pregnancy has NOT exceeded its 24th week and that the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman') available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/204071/HSA1-form.pdf which cites section 1(a) of the Abortion Act 1967.

Background

In the past, people with a gCSGV were identified from high-risk families where multiple individuals were affected by the same or related cancers. With the introduction of widespread genomic testing, these individuals may be identified by other routes, eg by histological subtype or tumour genomic sequencing. It is not known whether individuals who carry a classically high-penetrance gCSGV but lack a significant family history, have the same cancer risk as patients identified due to their high-risk family history. Furthermore, expansion of testing has led to the discovery of gCSGVs traditionally considered to be of 'moderate' penetrance in high-risk families, leading to uncertainty about the extent of their contribution to the observed cancer susceptibility in the family. The rapidly evolving complexity in this area has led to discrepancy in clinical practice and access to reproductive options for individuals and couples with a gCSGV.

Individuals and couples with a gCSGV have been using information about the known gene variant in the family to make reproductive decisions for many years. PND has been accepted for highly penetrant cancer susceptibility syndromes such as retinoblastoma (RB) and familial adenomatous polyposis (FAP) for several decades, although it is recognised that access throughout the UK may not be equitable.

In the UK, the Human Fertilisation and Embryology Authority (HFEA)[ii] regulates fertility clinics where human gametes or embryos are created and stored to aid couples with fertility issues, or tested, so families with serious genetic conditions can avoid passing on the condition to their children, under the terms of the Human Fertilisation and Embryology Act 1990 (as amended by the Human Fertilisation and Embryology Act 2008). This Act describes the licensing, inspection and standards that must be adhered to and covers PGT-M, including cancer susceptibility syndromes.

PGT-M was licensed for FAP in 2004, and for Lynch Syndrome (previously known as hereditary non-polyposis colorectal cancer, HNPCC) and hereditary breast and ovarian cancer (HBOC) due to *BRCA1* and *BRCA2* pathogenic gene variants in 2006. PGT-M is funded by the NHS in specific situations but other factors, eg geographical limitations, age, body mass index (BMI), smoking, can be barriers to accessing this NHS-funded treatment. PGT-M is a lengthy and demanding process which requires in-vitro fertilisation (IVF) and embryo biopsy, may entail significant costs to the couple if not provided for by the NHS, and may fail to achieve a pregnancy. In 2019, the largest provider of NHS-funded PGT-M, Guy's and St. Thomas' NHS Foundation Trust's PGT service reported a clinical pregnancy rate per PGT cycle of 30.4% and the clinical pregnancy per embryo transfer of 52.9%.[2]

[ii] The Human Fertilisation and Embryology Authority is the UK wider regulator of fertility treatment and embryo research. The HFEA support the issuing of guidelines to improve quality and consistency of care and information regarding reproductive choices for individuals living with cancer susceptibility syndromes.

Embryo testing and treatments can be used by people who have serious inherited diseases in their family and want to avoid passing the disease onto their children. It is possible to use PGT-M to test for almost any genetic condition where a specific gene is known to cause that condition. However, conditions can only be tested for when the condition has been considered by the HFEA to comply with legal criteria related to the risk of transmission and the seriousness of symptoms, in somebody affected by the genetic abnormality to be tested for.

European guidelines for prenatal clinical practice[3] aimed to provide a framework for prenatal diagnostic services, as well as addressing logistical considerations. The authors of this review, published in 2014, noted the lack of previous guidance and consensus information in this area.

The key recommendation of the European guidelines was that, through the provision of high-quality genetic counselling, individuals should find out about their risks and reproductive options at the time of predictive or diagnostic genetic testing for a gCSGV. If the individual/couple subsequently decide to proceed with PND or PGT-M, they should be supported effectively during the process, which should be organised efficiently by an appropriately trained HCP. If a decision is made to end the pregnancy, then this should be performed in a unit offering appropriate and sensitive care.

The importance of counselling and the effective discussion of reproductive options is a key theme in the literature.[4] In 2018, the Ethics Committee of the American Society for Reproductive Medicine (ASRM) published a practice committee document on the use of pre-implantation genetic testing for adult-onset conditions.[5]

The consensus of the ASRM was that due to the fact that the majority of these conditions manifest in adulthood, combined with variability of penetrance, thorough counselling is particularly important. A key recommendation from this document, and the previous ASRM practice committee opinion in 2008, was that PND should be discussed prior to decisions being made about PGT-M.[6] The ASRM concluded that PGT-M was ethically justifiable for serious adult-onset conditions when there were no known interventions, or the interventions were ‘significantly burdensome’. For lower penetrance conditions the consensus in the US was that PGT-M was still ethically acceptable as a matter of reproductive liberty.

The American College of Medical Genetics (ACMG) position statement on prenatal and pre-conception expanded carrier screening[7] also highlighted the importance of providing detailed and transparent information on conditions with mild phenotypes and variable penetrance. An important aspect of carrier testing, which is also relevant to cancer risk, is the remaining risk that a condition will manifest in the individual despite negative test results.

Despite this emphasis within published guidelines on the importance of communication between HCP and individuals/couples, there is evidence in the literature of widespread uncertainty, a range of personal viewpoints, and sometimes reluctance on the part of the HCP to discuss reproductive options with individuals who carry a gCSGV, as explored further below.

Experiences and views of healthcare professionals

Literature on views relating to PGT-M and PND for cancer susceptibility syndromes notes, perhaps not surprisingly, that HCPs hold a range of personal views.[8] Studies detail caution, unease and a range of concerns about offering testing for a gene that is not fully penetrant for a treatable disease common in the wider population, and of adult onset.[8–11] HCPs also raised concerns about the possibility of women choosing prenatal testing for 'information alone' rather than to inform the choice of termination, as they felt this could invade the privacy of the future child who would not then be able to make their own decision about predictive genetic testing.[8,10,11] In 2000, Lucassen and Houlston also found some evidence of directive counselling, dissuading women from pursuing prenatal testing for a *BRCA1* pathogenic gene variant.[8]

Nevertheless, HCPs generally expressed willingness to offer testing, despite any personally held reservations, with the choice ultimately being up to the individual/couple affected, after adequate counselling and consent.[8–10,12] Overall, HCPs supported reproductive autonomy and noted that the test could be of benefit to women and families with negative and traumatic personal experiences of cancer. HCPs also recognised that they should not deny or dismiss the seriousness of their patients' experiences with these conditions.[8,10,12]

The literature suggests that fetal medicine and clinical genetics teams are most familiar with requests for termination of pregnancy for structural, syndromic, chromosomal or single gene disorders 'which can readily be seen to carry a substantial risk of serious mental and/or physical handicap' (Ground E[iii] in Certificate A, form HSA1 reflecting section 1(d) of the UK Abortion Act 1967).[i,8]. Concerns held by HCPs regarding PND for cancer susceptibility may derive from a viewpoint 'which does not conform to the types of conditions typically seen and accepted in this context'.[11] HCPs did understand that termination of pregnancy could, alternatively, be offered under Ground C[iv] but were less familiar with this option, highlighting a potential training need.[8] Ground C states that 'the pregnancy has not exceeded its twenty-fourth week and that the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman…'. Indeed, because of the inherent risk associated with pregnancy, it has been argued that continuing a pregnancy *always* carries greater risk of physical injury to the woman than does termination, and that Ground C can therefore always be utilised if the pregnancy has not exceeded 24 weeks' gestation.

[iii] Ground E ('there is substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped') available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/204071/HSA1-form.pdf which cites section 1(d) of the Abortion Act 1967

[iv] Ground C ('the pregnancy has not exceeded its twenty-fourth week and that the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman') available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/204071/HSA1-form.pdf which cites section 1(d) of the Abortion Act 1967

From an emotional and psychological perspective, it can be readily argued that continuing a pregnancy in which the fetus may have inherited a gCSGV might, in some circumstances, carry a greater risk of injury to the mental health of the woman than the choice to terminate the pregnancy. This will depend on the personal and familial experiences of the woman and her own perspective. The 1967 Abortion Act does not demand that the practitioners signing certificate A in support of a termination (the abortion notification form required to be completed by two medical practitioners) have actual evidence that the Ground being used is supported, only that they have a belief that it is. In Great Britain, termination of pregnancy for a gCSGV is therefore legal and it is up to the clinicians signing certificate A to decide if they believe it is justified under Ground C.

In line with the 1967 Abortion Act, HCPs can conscientiously object to termination of pregnancy on moral or religious grounds but are still duty-bound to refer the individual to an alternative healthcare provider who will facilitate the wishes of the individual.

Clancy points out that attempts to reach consensus on a definition of severity in the context of PND and PGT-M have been unsuccessful, and 'may be unhelpful if it cannot take into account 'the woman's/couple's awareness and experience of the condition and the impact of the condition on affected individuals and their families'.[12]

Studies note the potential benefits of PND over PGT-M.[9,10] For example, Julian-Reynier *et al* note that PGT-M is a 'cumbersome process and only 25% of the couples benefiting from this procedure can expect to end up with a healthy child'.[9] In reality, centres offering PGT-M will explain that successful outcomes (the probability of taking home a healthy baby, conceived following PGT-M) are dependent on numerous factors including the age of the woman, her BMI and hormonal factors, as well as the experience and expertise of the unit offering this assisted reproductive technique. The pregnancy rates reported by clinics therefore vary widely and will be heavily dependent on the characteristics of the women seeking care.

Overall, therefore, HCPs were committed to providing care, often in spite of personal ethical reservations, and the strong need for national guidelines to support best practice in this area was widely emphasised.[11] Such guidelines would particularly help HCPs who feel ethically conflicted, or practically confused about offering PND and PGT-M in contexts such as cancer susceptibility.[9–11]

This range of HCP views and experiences, and lack of clarity in approach, was also reflected in the spectrum of experiences and attitudes reported from the patient perspective, as described in the next section.

Experiences and views of patients

While there is very limited literature exploring patient experience of undergoing PND or PGT-M for a gCSGV, there are more data highlighting attitudes towards PND and PGT-M (among other reproductive options) among patients with a gCSGV, with a particular focus on the views of women with *BRCA1* and *BRCA2* pathogenic gene variants.

There is evidence that for female carriers of *BRCA1* and *BRCA2* pathogenic gene variants, knowledge of their status had a significant impact on their reproductive views and behaviours, with many feeling pressured to make reproductive decisions quickly and prevent transmission of the gene variant to future generations.[13]

With regard to reproductive technologies, Chan *et al* (2017), in a survey of 1,081 self-reported *BRCA1* and *BRCA2* pathogenic gene variant carriers in the USA, found that 59% thought that PGT-M should be offered to carriers and 55.5% thought PND should be offered.[14] However, they also found that 20.6% of study participants did not know if they would consider ending a pregnancy after PND, highlighting the difficulty in deciding what they would theoretically do in these circumstances. Notably, several studies reinforced that access to PND and PGT-M was broadly supported by individuals with varying hereditary cancer susceptibility conditions.[15–18]

This support was expressed irrespective of whether they would use the technologies themselves, and indeed, many stated they would not use them, for a range of ethical, practical or financial reasons.[19–22] Termination of pregnancy was an area of particular difficulty. For example, a French study by Julian-Reynier *et al* (2012) found that although 32.5% and 50% of the 605 male and female *BRCA1* and *BRCA2* pathogenic gene variant carriers said they would undergo PGT-M or PND respectively, only 12.1% found termination of pregnancy acceptable. This was similarly reported by Ormondroyd *et al* in an English qualitative study (2012), although the findings were limited by small sample size.[9,23]

There were also differences in attitudes towards use of the technologies for susceptibility to different cancer types; for example a study in the Netherlands by Dommering *et al* (2017) found requests for prenatal diagnosis significantly higher among families affected by retinoblastoma than for other hereditary cancer syndromes, which the authors associate with retinoblastoma's early onset, high penetrance and lack of preventative surgery.[24] Similarly, Gregersen *et al*'s (2022) Danish study uncovered a strong desire among survivors of heritable retinoblastoma to prevent transmission of the condition to their offspring.[25] The nature of previous experience with cancer in the family was therefore significant in determining reproductive attitudes.

Despite these data, several studies draw attention to the widespread lack of knowledge of reproductive options among people with hereditary cancer susceptibility conditions, with many study participants reporting little or no knowledge of PGT-M or their option to use PND. [22,26–29]

Various suggestions were made to better improve access to the technologies. Julian-Reynier *et al* (2012) found that 85.4% of their research participants thought that information on PGT-M and PND should be systematically delivered alongside genetic test results.[9] However,

Donnelly *et al* (2013) instead argued that this needs to be delivered during pre-test counselling in order to be effective and meaningful.[30] Healthcare providers also need to be aware of the potential for patients to become overloaded with information and highlight the need to take into account a patient's absorptive capacity. Hurley *et al* (2012) suggested addressing this issue through the provision of written information to be taken away and read in the patient's own time.[31]

Concerns were raised by HCPs about patients potentially feeling a responsibility to use the technologies if their existence was brought up in consultations.[32,33] Indeed, the need for counselling, psychological support,[23] peer-to-peer support[25] and decision-aids[34] have all been strongly recommended, as well as the importance of ensuring patients have realistic expectations regarding the practical realities of PND and PGT-M, including physical demands and rates of successful outcomes.[13]

Consensus workshop

A virtual Zoom workshop was held on 6 November 2020 arranged by the BSGM Cancer Genetics Group (CGG) and the BSGM Fetal Genomics Group (FGG). It aimed to reach a consensus regarding when to offer PND and/or PGT-M for a gCSGV. Pre-and post-workshop surveys looked at care and/or opinion across UK, outlining discrepancies in practice and/or opinion throughout the UK about reproductive choices in patients with a gCSGV (see supplementary information).

Multidisciplinary members from the CGG and FGG identified delegates from across the UK in the fields of fetal medicine, clinical prenatal genetics, cancer genetics, PGT-M and ethics.

There was representation from the following professional groups and organisations:

- Antenatal Results and Choices (ARC), a charity supporting patients dealing with antenatal screening and investigations
- Association of Clinical Genomic Science (ACGS) representing Clinical Genetic Scientists within the NHS
- Association of Genetic Nurses and Counsellors (AGNC)
- British Maternal and Fetal Medicine Society (BMFMS) representing Consultants in Fetal Medicine
- Clinical Genetics Society (CGS) representing consultants in clinical genetics
- Genetic Alliance UK, a charity that works on a variety of issues facing individuals and families with genetic conditions
- Human Fertilisation and Embryology Authority (HFEA)
- Ovarian Cancer Action (OCA), a charity funding research on the detection, prevention and treatment of ovarian cancer
- PHG Foundation (PHGF), which helps policy makers understand how new technologies can improve healthcare and how to implement them
- Progress Educational Trust (PET), a charity that seeks to improve choices for people affected by infertility and genetic conditions
- RCOG (RCOG) representing consultant obstetricians and gynaecologists.

The workshop involved presentations from experts about PGT-M, PND and gCSGVs in the morning followed by multidisciplinary breakout groups with a facilitator in the afternoon. The breakout groups discussed previously agreed key issues identified by the CGG and FGG in developing UK guidance for PND and PGT-M for gCSGVs. Outcomes from the breakout groups were then discussed among all the workshop delegates and areas of consensus and contention noted.

The following areas of consensus were identified:

1. Individual's and couple's thoughts about their reproductive choices in relation to gCSGVs should be sought, explored, and respected during the predictive or diagnostic genetic testing process.
2. There is presently disparity across the UK regarding if and when reproductive options are discussed with individuals and couples who have cancer susceptibility syndromes during their predictive and diagnostic genetic testing process.
3. It is helpful to move away from the concept of 'offering' PND or PGT-M to instead 'discussing' these reproductive options with individuals and couples when they are undergoing predictive or diagnostic genetic testing.
4. There is a lack of national consensus guidance to support HCP and individuals/couples in their decision-making.
5. It is vital that the individual's/couple's perspective is ascertained during their predictive and diagnostic testing for cancer susceptibility conditions as:
    a. Individuals/couples wishing to pursue PND or PGT-M often have far-reaching personal and familial experiences motivating their decision.
    b. Individuals/couples may express a sense of obligation to prevent a repetition of such experiences in future generations.
    c. These experiences should not be taken lightly or go unacknowledged by HCPs.
6. As there is a lack of national consensus guidance regarding reproductive options for cancer susceptibility conditions:
    a. There is a risk that HCPs will fail to discuss reproductive options for gCSGVs, in particular if there is a new request where the department has not facilitated PND or PGT-M for the condition before.
    b. There is a need for transparent and objective processes with clear lines of accountability and multidisciplinary input to support reproductive decision-making.
    c. Information and counselling about pathways should be available to individuals and couples during the predictive and diagnostic testing pathway, eg PGT-M or non-invasive fetal sexing (NIPD) followed by invasive testing if appropriate.

Following the workshop, three workstreams were set up with appropriate multi-professional and lay member representation to address the following unresolved areas of contention:

1. Moderate penetrance genes
2. Sex-specific variable penetrance genes
3. Facilitation of reproductive options

Outputs from these three workstreams were then used to develop a genetic counselling framework for HCP involved in the care of individuals/couples with a gCSGV in relation to their reproductive options. Appendix 2 lists the group membership of the workstreams.

UK-wide surveys of genetic laboratories, clinical genetics and fetal medicine departments were also performed to identify current practice for PGT-M and PND for gCSGVs (See Supplementary Information). These highlighted difficulties in accessing current or retrospective clinical and laboratory practice data and the need for iterative review and audits in this area.

Moderate penetrance genes

For the purposes of this guidance document, the conditions listed in Appendix 3 have been taken from the National Genomic Test Directory (https://www.england.nhs.uk/publication/national-genomic-test-directories) and are considered to be well-characterised conditions with high cancer penetrance.

However, for couples who have a cancer susceptibility syndrome that is not classically associated with high risk, but instead is of moderate penetrance, understanding of genotype/phenotype correlation may be limited. Additionally, the patient's familial experience of cancer may not concur with available literature regarding penetrance. For example, there may be more cancer observed in the family than would ordinarily be expected with a pathogenic variant in that gene. Current cancer genetics knowledge in this context may not provide clear predictive information for patients about the probability of future cancer risk or necessarily concur with the individual/couple's perception of risk. Evidence-based assessment programmes, such as CanRisk, can be helpful in personalising risk assessments in this situation. However, CanRisk (and other risk assessment tools) cannot currently input all gCSGVs. Furthermore, the use of specific cancer penetrance thresholds that ignore personal circumstances are not helpful. It would therefore be difficult and undesirable to be prescriptive about which genes should, or should not, be available for PND or PGT-M.

Appendix 4 outlines the specific moderate-penetrance genes discussed in the consensus workshop. However, the guidance provided in this document applies to any gene considered to be of moderate penetrance based on current literature at the time of the individual/couple's consultations with their genetic/genomic HCP.

An HFEA licence is required for each new condition where PGT-M is being considered. If a PGT-M centre has applied for and been granted a licence for a particular genetic condition then PGT-M may be undertaken without a further application. The licensing process involves submitting an application to the HFEA which is sent for formal external review by geneticists, relevant support groups, lay-people and HFEA advisors. From the results, a panel decides if the condition should be licensed for PGT-M. In deciding whether to authorise PGT-M for a new genetic condition or disorder, the HFEA has to be satisfied that the embryo(s) is at risk of having a heritable condition; then, if so, that the genetic, chromosomal or mitochondrial disease or disorder is serious. The HFEA does not look at how the genetic, chromosomal, mitochondrial disease or disorder affects a particular family but, instead, looks at how the disorder affects a person in the worst-case scenario.

Alongside this check that the condition is generally authorised for PGT-M, the HFEA requires any clinic considering providing PGT-M for a condition to undertake a case-specific review of the significance of risk of transmission of the gene variant to be tested for, and of the likely prevalence of severity of symptoms in somebody inheriting the gene variant. This is undertaken to ensure that each case meets the legal criteria for PGT-M to be applied. It allows consideration of the pathogenicity of the specific gene variant in the case, along with any other case-specific variables.

Ethical distinctions have been made regarding the appropriateness of PND when compared with PGT-M for moderate penetrance gCSGVs, ie is it ethically more acceptable to perform PGT-M for a moderate penetrance gCSGV than it is to perform PND and subsequent termination of pregnancy? However, again, this may not be a helpful approach for specific individuals/couples who may have many factors guiding their reproductive decision-making. Some may feel strongly that they wish to avoid passing on the gCSGV to future children but, for example, they may not be eligible for PGT-M, or they may wish to establish a pregnancy naturally rather than embark on lengthy IVF treatment which may not be successful.

In light of this complexity, it is essential that counselling regarding prenatal reproductive decisions for moderate risk gCSGVs is provided by genetic/genomic HCP with expertise in this area. Information should be given and presented without bias. Although HCP and lay group members are of the opinion that very few individuals/couples would seek PND or PGT-M in relation to a moderate risk gCSGV, careful and sensitive genetic counselling regarding these reproductive options should be offered.

Sex-specific variable penetrance genes

There are some cancer susceptibility syndromes where, currently, the cancer risk is thought to be primarily for breast and/or gynaecological cancer in women and there is no or minimal increase in cancer risk for men with the gCSGV, for example, pathogenic variants in the genes *BRCA1* and *PALB2*. However, there will be an increase in cancer risk to female offspring of these men if they inherit the gCSGV. Appendix 5 provides examples of this category of cancer susceptibility genes. However, the guidance provided in this document applies to any gene considered to have sex-specific variable penetrance based on current literature at the time of the individual/couple's consultations with their genetic/genomic HCP.

The literature in relation to patient and HCP attitudes regarding PND and PGT-M in this setting is scarce. However, the same principles apply as those followed for PND and PGT-M for gene variants with moderate penetrance. It is likely that requests for termination of pregnancy for sex-specific variable penetrance gCSGVs where the fetus is of the sex with no or minimal increased risk will be infrequent. In line with the previous discussion however, these could only be justified under Ground C.

For genes with sex-specific variable penetrance, individuals/couples have two possible options if they choose to have PND (see figure in Appendix 1)

- Some individuals/couples may choose to have PND and testing for the gCSGV only. These individuals/couples may choose not to continue a pregnancy if the fetus has the gCSGV, regardless of the sex of the fetus. In this situation, testing for the gCSGV only is required.
- Individuals/couples, who wish to continue a pregnancy if the fetus is male and carries the gCSGV, could have fetal sexing at 9–10 weeks gestation, which is carried out on blood from the pregnant woman. If the fetus is female, they could choose to opt for invasive testing and, if the female fetus carries the gCSGV, to not continue the pregnancy.

With regard to PGT-M for gCSGVs with sex-specific variable penetrance, the option should be discussed with couples as part of the genetic counselling process, including caveats regarding availability, timelines and eligibility. Consideration should be given to whether the individual is at an age where pregnancy is likely to be possible with PGT-M and how this likelihood may differ from natural conception.

Under HFEA regulation, individuals/couples can choose to exclude all embryos carrying the gCSGV or to have male embryos with the gCSGV transferred, even if it is currently thought the cancer risk in males is not significantly increased. Centres offering PGT-M need to try to maximise patient choice while ensuring careful counselling, so couples are aware that choosing an option that excludes male embryos carrying the gCSGV will reduce the embryos available for transfer from 75% to 50%, thus decreasing the chance of having a healthy child born from the process of PGT-M.

Genetic counselling framework

Counselling of individuals/couples with a gCSGV regarding their reproductive options should cover but is not limited to the following:

- An individual/couple's understanding of the risk associated with the gCSGV (the discussion should be directed by the meaning a gCSGV has for the individual/couple within their family context)
- To what degree the gCSGV in a family is thought to account for the observed cancer risk, eg there may be additional cancers present in the family which are not known to be associated with the gCSGV
- Current knowledge about the gCSGV's penetrance, including how it may be influenced by sex, other genetic and non-genetic factors
- Expected age of onset/severity of disease associated with the gCSGV
- Honest communication about potential outcomes or ability to predict chance of outcomes
- Surveillance that might be available to facilitate early diagnosis of malignancies or risk-reduction options, such as surgery, to prevent disease
- Horizon scanning for treatments/improvements in cancer management/prognosis and prevention
- Gentle exploration about possibility of decision regret
- Support for the individual's/couple's decision-making and choice
- PND should only be undertaken if the couple plan to end the pregnancy if the fetus is affected, not as a means of predictive testing for a cancer susceptibility condition because this is not generally offered for most of these conditions in childhood. This approach is suggested in order to protect the unborn person's autonomy to decide if and when they want to find out their own status in the future.

Some patients may change their mind about termination after a positive test, thereby effectively providing a test result for the child, once born, for an adult-onset condition. HCPs need to remain non-judgemental and stay connected with families if patients decide not to terminate after a prenatal test. Literature regarding experience in Huntington's disease shows that parents disengaged with genetics if they did not follow through with terminating an affected pregnancy.[38]

Appendix 6 provides a link to a detailed framework for genetic/genomic HCPs to enable supportive, non-directive consultations with individuals/couples about their options.

Consensus guidance

- PND and PGT-M should be discussed with all individuals/couples who are at risk of having a child with a gCSGV to ensure they are aware of all their reproductive options and can make an informed choice about which avenue is best for them. Children at risk of a cancer susceptibility condition should be advised to seek referral in adulthood, if they wish, when they are thinking about predictive testing or planning a family, in order to discuss the reproductive options available to them.
- As well as PND and PGT-M, it is helpful for individuals/couples to consider all reproductive options during the predictive or diagnostic genetic testing process, including choosing not to undergo any prenatal testing, adoption, gamete donation, and not to have children. It is also important to be clear that such information has a potential impact on the whole family and extended family members. Appendix 6 includes a link to a reproductive information leaflet that may be used to facilitate information-giving.
- There should be a secure and contemporaneous record of the discussions relating to reproductive options with individuals/couples during the predictive or diagnostic genetic testing process by an appropriately trained genetic/genomic HCP for all gCSGVs (whether they are associated with moderate or high cancer risk).
- Individuals/couples with a gCSGV may choose to undergo testing to enable choice of management options in the future, including reproductive options and those of their families.[30,35]
- Reproductive decision-making in individuals/couples with a cancer susceptibility syndrome is complex.[36] It requires highly skilled professionals who can support individuals/couples in a challenging process of reconciliation with a wide variety of considerations and emotions regarding their reproductive wishes.[37] Consideration should be given to using a checklist during consultations which includes discussion of reproductive options for individuals/couples.
- Appendix 6 provides a genetic counselling framework for appropriately trained genetic/genomic HCPs to support the consultations they may have with individuals/couples in this setting and ensure all relevant aspects have been considered. At the current time, appropriately trained genetic/genomic HCPs would be defined as registered genetic counsellors and clinical geneticists with experience of reproductive counselling and cancer genetics, thus consultations may sometimes require two colleagues working together with these specialist skills.
- It is good practice to discuss all cases of PGT-M and PND for a gCSGV in a multidisciplinary forum, and is essential in cases of gCSGV with moderate penetrance and sex-specific variable penetrance gCSGVs or where the primary HCP has concerns about the understanding of the individual/couple regarding their options, or where the HCP feels conflicted due to their personal views. Outcomes from the multidisciplinary discussion should be clearly documented within the individual/couple's medical records and conveyed to them in a timely way.

- Multidisciplinary teams should include representation from cancer genetics, prenatal genetics and fetal medicine. If PGT-M is being considered, then PGT genetics, assisted conception unit and PGT laboratory colleagues should also be involved. Consultation with the local clinical ethics committee, the FGG and/or the Genethics Forum may also be helpful.
- For PND, individuals/couples need information about the process of testing including the miscarriage risk, that testing may be possible from 11 weeks' gestation by chorionic villus sampling (CVS), or from 15–16 weeks' gestation by amniocentesis, the turnaround time for testing and obtaining results, the 'pros and cons' of testing and information on which professional will feedback the results, which at the current time is recommended to be a genetic/genomic HCP with expertise in this area. Fetal medicine HCPs should be aware of this guidance and be prepared to facilitate the process of PND if requested following reproductive counselling of the individual/couple in clinical genetics.
- In order to ensure that a timely referral for PND is made, it is suggested that individuals/couples with a gCSGV should be given contact details for their regional genetics service, so they can approach them when contemplating or conceiving a pregnancy. Furthermore, all women should be asked at their antenatal booking appointment whether there is a 'genetic condition' in the family. A positive response should precipitate an urgent referral to their regional clinical genetics service.
- Reproductive counselling for a gCSGV should ideally be performed pre-conception, so PGT-M is still an option, or at the latest in the first/early second trimester of a pregnancy.
- Individuals/couples need to be clear that they would not continue with the pregnancy if the fetus carried the gCSGV, before opting for invasive prenatal testing. Signposting individuals/couples to charities that help with decision making around prenatal testing such as Antenatal Results and Choices (ARC) can be beneficial. HCPs should understand that, despite intentions, patients may change their mind regarding termination of pregnancy after PND, and continue to maintain connection with a family where possible should this occur.
- PND should be completed within the first or early second trimester to enable individuals/couples, who decide to end the pregnancy, to do so before 24 weeks' gestation under the Abortion Act using Certificate A form HSA1 and citing Ground C.
- In the unlikely event of a positive prenatal molecular result after 22 weeks' and before 24 weeks' gestation, a fetocide would be necessary but should still be performed under Ground C.
- After 24 weeks' gestation, the Abortion Act allows termination to be supported by two registered medical practitioners under Ground E if; a) the women has a life-threatening illness or b) the fetus has a pathology that carries a substantial risk of significant handicap. It is highly unlikely that a gCSGV would be considered to confer these risks.
- With regard to PGT-M, individuals/couples need information about the benefits and limitations of the process, such as timelines, personalised information, including the importance of age, fertility history, medical factors for the male or female partner that may complicate success of them having an unaffected child from the process and

whether they are eligible for NHS funding. They also need to be informed about options if they do not fulfil NHS eligibility criteria, which vary slightly throughout the UK.

> The current PGT-M criteria are listed in the links below:

NHS England Clinical Commissioning Policy: Pre-implantation genetic diagnosis (April 2014)

NHS National Services Scotland: Pre-implantation genetic diagnosis (April 2022)

NHS Wales Specialised Services Policy on pre-implantation genetic diagnosis (August 2014).

Please note, the PGT-M eligibility criteria in England are currently under review.

> PGT-M can only be performed if the HFEA has licensed that condition, so it is vital the genetic/genomic HCP involved in diagnostic or predictive testing checks that a licence has been granted for PGT-M for that condition. This information is available on the HFEA website. The Online Mendelian Inheritance in Man (OMIM) condition number (not the OMIM gene number), as well as the condition name, can be used to search the database.

> If the condition does not appear on the list, then the genetic/genomic HCP should check with the NHS PGT-M centre whether a licence application to the HFEA would be possible for the condition. It is important if individuals/couples want to explore PGT-M that they are aware of the NHS PGT-M eligibility criteria and meet those criteria for their area of the UK. Self-funding and private PGT-M may also be available for couples who do not meet NHS eligibility criteria. Couples contemplating PGT-M also need to be aware of the extended timeframes that are likely to be involved, particularly if it is necessary to apply to the HFEA for a licence before treatment can begin.

Please note, with regard to current funding at the time of publication of this guidance: Fetal sexing under NHS England is funded and PND is funded across the UK. PGT-M is funded based on meeting the NHS England/Welsh/Scottish or Irish PGT criteria. NIPD for gCSGV is not currently funded through NHS England's national genomic test directory and the NHS. There is an option for self-funded bespoke NIPD to be developed (ideally prior to conception) if the condition is carried by the male partner or if both parents carry different variants in a recessive cancer susceptibility condition.

Conclusion

Our understanding of the genomic architecture of cancer susceptibility has rapidly evolved in the past decade. Alongside this expanding knowledge, there has been an acknowledgement of the growing complexity of cancer risk assessment for individuals and families who carry a gCSGV.

Although there have been significant advances in the management of hereditary cancer, an important minority of individuals/couples may have personal or familial experiences that motivate them to consider the options of PND and PGT-M.

Our UK-wide surveys of practice in this area and the outcomes from the joint CGG/FGG consensus workshop demonstrate inequitable access to PND and PGT-M for affected individuals/couples and significant disparities regarding the use of these reproductive options in the context of a gCSGV.

This joint CGG/FGG consensus guidance provides HCPs with a clear counselling framework to help support individuals/couples during their decision-making process in this complex and emotive area. The aim is that, in turn, this will translate into a growing confidence and experience so that robust, equitable and ethical pathways are available across the UK for individuals/couples who choose to access these reproductive options for cancer susceptibility conditions.

Glossary

Germline cancer susceptibility gene variant (gCSGV) is a change (variant) in a gene that confers an increased risk of developing cancer for the individual who carries it. For the purposes of this guidance, gCSGV only refers to pathogenic (Class 5) or likely pathogenic (Class 4) variants.

Pathogenic gene variant is a gene change that increases an individual's susceptibility to a specific condition.

Prenatal diagnosis (PND) refers to diagnostic procedures carried out during pregnancy in order to detect the presence of genetic or other abnormalities in the developing fetus. Examples of procedures include ultrasound scanning, non-invasive PND, amniocentesis and chorionic villus sampling.

Non-invasive prenatal diagnosis (NIPD) involves taking blood from a pregnant woman for analysis of cell-free DNA in order to perform a diagnostic test, to confirm or exclude a specific condition. This can be performed from 9–10 weeks and has no associated miscarriage risk.

Amniocentesis is a procedure in which a small amount of amniotic fluid is removed with a needle from the sac surrounding the fetus. It can be performed from 15–16 weeks' gestation.

Chorionic villus sampling (CVS) involves sampling and testing a piece of the placenta to determine fetal characteristics, by passing a needle into the mother's abdomen. This test can be performed from the 11th week of pregnancy.

Monogenic disorders are caused by pathogenic variation in a single gene and are typically recognised by their familial inheritance patterns.

Pre-implantation genetic testing for monogenic disorders (PGT-M) can be performed on cells from early embryos created by in vitro fertilisation (IVF) so that those with a particular genetic condition are not transferred into the uterus. Also referred to as pre-implantation genetic diagnosis (PGD).

Penetrance is the proportion of individuals carrying a particular gene variant (the genotype) that also express an associated trait (the phenotype).

Sex-specific variable penetrance is when the likelihood of the phenotype manifesting in an individual with a gene variant differs depending on their sex or their sex assigned at birth.

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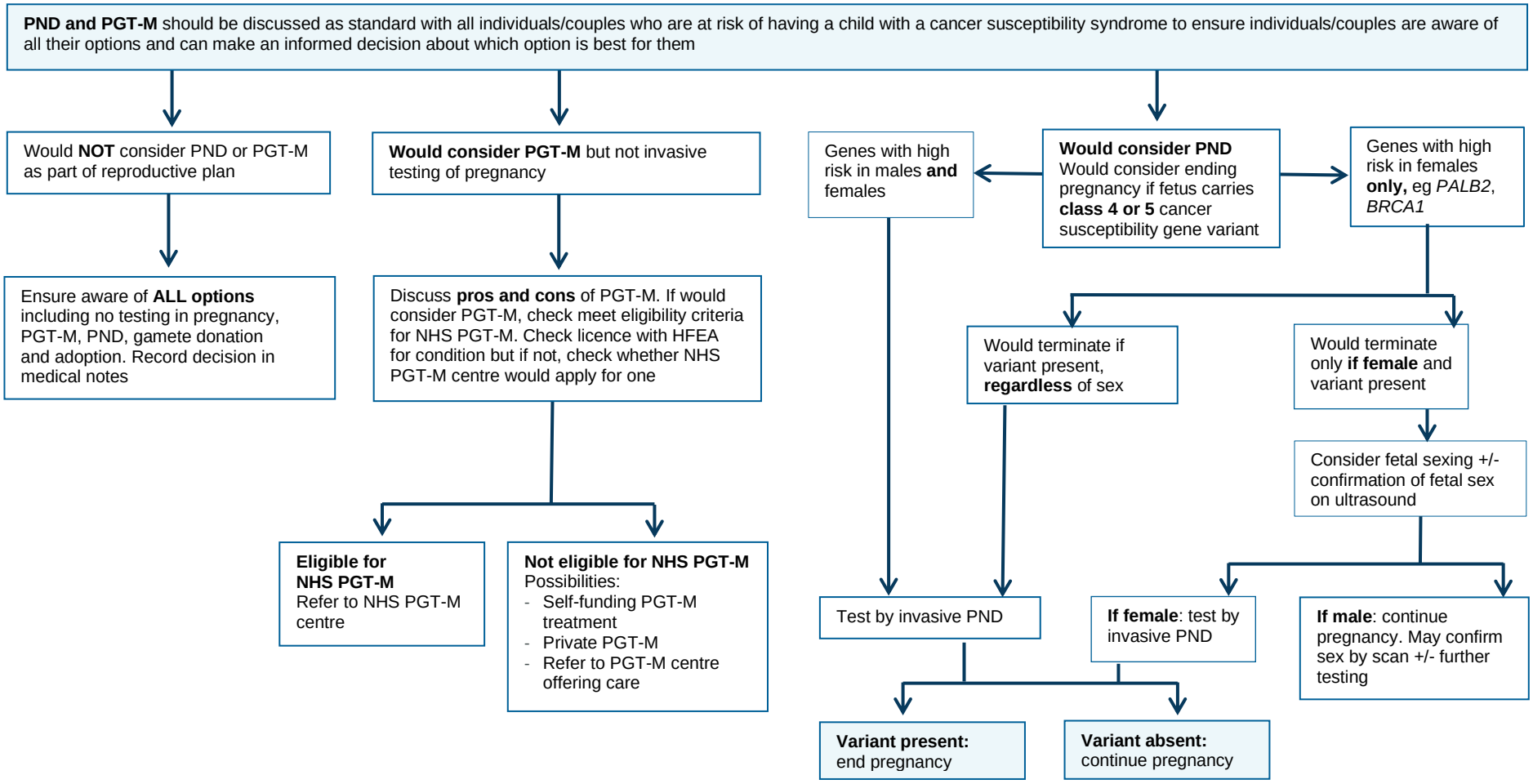
Appendices

Appendix 1: Reproductive options for individuals and couples with a gCSGV

See text for details regarding termination under Ground C under 24 weeks of pregnancy



Appendix 2: Workstream members

Workstream 1: Sex-specific variable penetrance

Name	Roles/representing
Angela Brady (chair)	Cancer and Prenatal Genetics
Rhianna Rakhra	Prenatal/PGT / Genetic Counsellor
Carol Gardiner	Prenatal Genetics / FGG
Matilda Bradford	Genetic Counsellor
Rachel Liebling	Fetal Medicine
Mari Jones	Genetic Counsellor
Sandy Starr	Progress Educational Trust
Helen White	CanGene-CanVar Patient Reference Panel representative
Sara Lykke Madsen	ARC representative
Pam Renwick	ACGS representative
Vinod Varghese	Cancer and Prenatal Genetics

Workstream 2: Moderate penetrance genes including dominant-recessive overlap

Name	Roles/representing
Lorraine Cowley (Chair)	Genetic Counsellor / Cancer Genetics
Amy Taylor	Cancer Genetics / CGG / Genetic Counsellor
Alec McEwan	Fetal Medicine / BMFMS
Alison Hall	PHG Foundation
Emma Kivuva	Prenatal Genetics / PGT
Nick Meade	Genetic Alliance
Julie Young	CanGene-CanVar Patient Reference Panel representative
Jane Fisher	ARC representative
Lowri Hughes	ACGS representative
Fiona McKay	NIPD service lead at Great Ormond Street Hospital
Gayle Vincent	Genetic Counsellor in PGT and Cancer

Workstream 3: Facilitation of reproductive options

Name	Roles/representing
Alison Male (chair)	Prenatal Genetics / FGG chair
Anju Kulkarni	Cancer Genetics / CGG
Tazeen Ashraf	Prenatal Genetics
Mark Kilby	Fetal Medicine
Sianan MacParland	Genetic Counsellor / Northern Ireland
Samantha Doyle	Prenatal Genetics
Caroline Dale	CanGene-CanVar Patient Reference Panel representative
Hannah McInnes-Dean	ARC representative
Judy Chow	ACGS representative
Felicity Boardman	Professor of Social Science in Genomics

Appendix 3: High penetrance cancer susceptibility genes

These conditions have been taken from the National Genomic Test Directory for rare and inherited disease (Note: this table refers to version 1 of the directory available on the NHS England website in April 2021).

Clinical indication ID	Clinical indication	Test ID	Target/genes (PGT-M OMIM number)
R207	**Inherited ovarian cancer (without breast cancer)**	R207.2	*BRCA1 (113705); BRCA2 (600185 & 612555); PALB2 (610355) MLH1, MSH2; MSH6 (all approved without OMIM number);*
R208	**Inherited breast cancer and ovarian cancer**	R208.1	*BRCA1(113705); BRCA2 (600185 & 612555); PALB2 (610355)*
R211	**Inherited polyposis**	R211.2	*APC (175100); BMPR1A (174900); MUTYH (608456); PTEN (601728, 158350 & 605309; SMAD4 (174900); STK11 (175200) MLH1; MSH2; MSH6 PMS2 – all approved without OMIM number*
R212	**Peutz-Jeghers syndrome**	R212.1	*STK11 (175200)*
R213	**PTEN Hamartoma tumour syndrome**	R213.1	*PTEN (601728, 158350 & 605309)*
R214	**Nevoid basal cell carcinoma syndrome or Gorlin syndrome**	R214.1	*PTCH1 (109400); SUFU (109400)*
R215	**CDH1-related cancer syndrome**	R215.1	*CDH1 (137215)*
R216	**Li Fraumeni syndrome**	R216.1	*TP53 (151623)*
R217	**Endocrine neoplasia**	R217.1	*MEN1 (131100)*
R218	**Multiple endocrine neoplasia type 2**	R218.1	*RET (171400)*
R219	**Retinoblastoma**	R219.1	*RB1 (180200)*
R221	**Neurofibromatosis type 2**	R221.1	*NF2 (101000)*
R223	**Inherited predisposition to paragangliomas**	R223.2	*SDHB (115310); SDHD (168000) Note: there is a parent of origin effect for SDHD*
R225	**Von Hippel-Lindau syndrome**	R225.1	*VHL (193300)*
R221	**Schwannomatosis**	R393.1	*SMARCB1 (162091); LZTR1 (162091)*

Appendix 4: Examples of moderate risk cancer susceptibility genes

Gene	Dominant phenotype (heterozygous variant)	Recessive phenotype (homozygous or compound heterozygous variants)	References
ATM	Moderate risk of breast cancer in women. Relative risk 2–4 compared to general population Specific variants (eg c.7217T>G) confer a high risk and are managed as for eg *BRCA2* Frequency 1:100–1:150	Causes ataxia telangiectasia (AT), a neurodegenerative disorder with immunodeficiency and an increased risk of developing cancer Often diagnosed during childhood due to ataxia, slurred speech, frequent infections Lifetime risk of cancer in classic AT ~38%, mostly leukaemia and lymphoma in childhood Cancers in adulthood include ovarian cancer, breast cancer, gastric cancer, melanoma, leiomyomas, and sarcomas Life expectancy considerably reduced Prevalence 1:40,000–1:100,000 live births in the US, varies with degree of consanguinity	GeneReviews for AT https://www.ncbi.nlm.nih.gov/books/NBK26468/ Breast cancer risk review: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5927797/
PMS2	One of four genes that cause Lynch syndrome, but confers lower cancer risks than other Lynch syndrome genes Cancer risks not significantly increased until age 40 Bowel cancer lifetime risk ~13% compared to ~6% in general population Women also have ~13% risk of endometrial cancer compared to ~3% in general population Frequency ~1:700	Causes constitutional mismatch repair deficiency (CMMRD), a rare childhood cancer predisposition syndrome Presents with childhood onset of cancer including brain tumours, intestinal and blood cancers Few affected individuals survive to adulthood	GeneReviews for Lynch syndrome https://www.ncbi.nlm.nih.gov/books/NBK1211/ Review of CMMRD: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6226037/

Gene	Dominant phenotype (heterozygous variant)	Recessive phenotype (homozygous or compound heterozygous variants)	References
RAD51C and RAD51D	Increased risk of ovarian cancer for women (~11% compared to ~2% in general population) Moderate risk of breast cancer in women (~17–30% lifetime risk compared to 12% in general population)	For RAD51C – one of the causes of Fanconi anaemia, a rare childhood-onset condition causing physical abnormalities, bone marrow failure, and high risk of cancer Early onset, life expectancy considerably reduced Very rare, few case reports	GeneReviews for Fanconi anaemia: https://www.ncbi.nlm.nih.gov/books/NBK1401/ Breast and ovarian cancer risks for *RAD51C* & *RAD51D*: https://academic.oup.com/jnci/article/112/12/1242/5764125
BRIP1	Increased risk of ovarian cancer for women (~5–10% compared to ~2% in general population) Possible moderate risk of breast cancer, currently unclear	One of the causes of Fanconi anaemia, a rare childhood-onset condition causing physical abnormalities, bone marrow failure, and high risk of cancer Early onset, life expectancy considerably reduced Very rare, accounts for ~2% of patients with Fanconi anaemia	GeneReviews for Fanconi anaemia: https://www.ncbi.nlm.nih.gov/books/NBK1401/
BAP1	Increased risk of: - uveal (eye) melanoma, 16–36% - BAPoma & melanoma (skin tumours) - mesothelioma (lung cancer), 19–25% - renal cell (kidney) cancer, ~10% Possible also increased risk of meningioma, basal cell carcinoma (BCC), and cholangiocarcinoma Approx 85% lifetime risk of at least one cancer	Not reported	GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK390611/ *BAP1* review: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6292796/

Gene	Dominant phenotype (heterozygous variant)	Recessive phenotype (homozygous or compound heterozygous variants)	References
FH	Causes hereditary leiomyomatosis and renal cell cancer (HLRCC) Renal cancer affects ~15% but can occur at young ages and has poor prognosis Cutaneous leiomyomata affect ~50%, not malignant Uterine leiomyomata (fibroids) affect ~90% of women, rarely malignant transformation	Causes fumarate hydratase deficiency Results in severe neonatal and early infantile encephalopathy leading to failure to thrive, hypotonia and seizures	GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1252/ Fumarase deficiency review https://pubmed.ncbi.nlm.nih.gov/33052056/
SDHx (not including SDHB and SDHD)	Increased risk for paragangliomas and phaeochromocytomas	Reported for *SDHB* and *SDHD* but not for other *SDHx* genes	GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1548/

Appendix 5: Examples of sex-specific variable penetrance cancer susceptibility genes

Gene	Female cancer risks	Male cancer risks	References
BRCA 1	High risk of breast cancer – 72% (95% CI 65-79%) up to age 80 years (compared to ~12% in general population). Risk starts to rise significantly from age 30 years.	Minimal increased risk for male breast cancer – 0.4% (95% CI 0.1–1.5%) risk up to age 80 years compared with <0.1% in general population. Risk of prostate cancer not significantly increased compared with general population risk.	Kuchenbaecker *et al* 2017: https://pubmed.ncbi.nlm.nih.gov/28632866/ Li *et al* 2022: https://pubmed.ncbi.nlm.nih.gov/35077220/
BRCA 2	High risk of breast cancer – 69% (95% CI 61-77%) up to age 80 years (compared to ~12% in general population). Risk starts to rise significantly from age 30 years.	4% (95% CI 2–8%) risk up to age 80 years for breast cancer compared with <0.1% risk in general population. 27% (95% CI 21–35%) risk up to age 80 years for prostate cancer compared with 18% risk in general population.	Kuchenbaecker *et al* 2017: https://pubmed.ncbi.nlm.nih.gov/28632866/ Li *et al* 2022: https://pubmed.ncbi.nlm.nih.gov/35077220/
PALB2	High risk of breast cancer – 53% (95% CI 44–63%) up to age 80 years (compared to ~12% in general population). Absolute risks influenced by cancer family history.	1% (95% CI 0.2–5%) risk up to age 80 years compared with <0.1% risk in general population.	ACMG clinical practice resource: https://pubmed.ncbi.nlm.nih.gov/33976419/
MSH6	One of four genes that cause Lynch syndrome. Endometrial cancer lifetime risk ~41% compared to ~3% in general population. Ovarian cancer lifetime risk ~11% compared to ~2% in general population. Colorectal cancer lifetime risk ~20% compared to ~6% in general population.	Minimal increased risk of non-colorectal cancer Colorectal cancer lifetime risk ~18% compared to ~7% in general population.	Prospective Lynch Syndrome database – Dominguez-Valentin *et al* 2019: https://pubmed.ncbi.nlm.nih.gov/31337882/

Appendix 6: Supplementary resources

A range of useful supplementary material is available to view and download, including:

- Genetic Counselling Framework
- Patient leaflet on reproductive options for cancer susceptibility gene variants
- UK national responses to a survey on prenatal testing and PGT-M: testing for cancer predisposition syndromes, March 2020

The following documents are available from the members area of the BSGM website:

- Prenatal diagnosis experience for CSGVs from 10 genetic centres in the UK
- Experience to date with PGT-M for cancer susceptibility conditions

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