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GUIDELINE

Management of patients with germline predisposition to haematological malignancies considered for allogeneic blood and marrow transplantation: Best practice consensus guidelines from the UK Clinical Genetics Group (UKCGG), CanGene-CanVar, NHS England Genomic Laboratory Hub (GLH) Haematological Malignancies Working Group and the British Society of Blood and Marrow Transplantation and cellular therapy (BSBMTCT)

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Summary

Germline predisposition to haematological cancers is increasingly being recognised. Widespread adoption of high-throughput and whole genome sequencing is identifying large numbers of causative germline mutations. Constitutional pathogenic variants in six genes (DEAD-box helicase 41 [*DDX41*], ETS variant transcription factor 6 [*ETV6*], CCAAT enhancer binding protein alpha [*CEBPA*], RUNX family transcription factor 1 [*RUNX1*], ankyrin repeat domain containing 26 [*ANKRD26*] and GATA binding protein 2 [*GATA2*]) are particularly significant in increasing the risk of haematological cancers, with variants in some of these genes also associated with non-malignant syndromic features. Allogeneic blood and marrow transplantation (BMT) is central to management in many haematological cancers. Identification of germline variants may have implications for the patient and potential family donors. Beyond selection of an appropriate haematopoietic stem cell donor there

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may be sensitive issues surrounding identification and counselling of hitherto asymptomatic relatives. If BMT is needed, there is frequently a clinical urgency that demands a rapid integrated multidisciplinary approach to testing and decision making involving haematologists in collaboration with Clinical and Laboratory Geneticists. Here, we present best practice consensus guidelines arrived at following a meeting convened by the UK Cancer Genetics Group (UKCGG), the Cancer Research UK (CRUK) funded CanGene-CanVar research programme (CGCV), NHS England Genomic Laboratory Hub (GLH) Haematological Oncology Malignancies Working Group and the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT).

KEYWORDS
BMT, germline cancer predisposition, transplant donor selection, Leukaemia

INTRODUCTION

Heritable predisposition to haematological malignancy

There is a growing recognition that constitutional pathogenic and likely pathogenic (P/LP—Class 4 and 5) variants in certain genes are associated with a significantly increased risk of haematological malignancy, often combined with other non-malignant phenotypic features. Compelling evidence has shown an association between genes causing syndromes with a high risk of non-haematological features, such as heritable tumour protein p53 (TP53)-associated syndromes, including Li Fraumeni syndrome (*TP53*), ataxia-cytopenia syndrome (sterile alpha motif domain-containing 9-like [*SAMD9L*]) or certain telomeropathies (telomerase reverse transcriptase [*TERT*], telomerase RNA component [*TERC*]) and haematological neoplasia. In addition, P/LP (Class 4 and 5) variants in six genes are increasingly recognised to be associated with a haematological-predominant phenotype (DEAD-box helicase 41 [*DDX41*], ETS variant transcription factor 6 [*ETV6*], ankyrin repeat domain containing 26 [*ANKRD26*], GATA binding protein 2 [*GATA2*], CCAAT enhancer binding protein alpha [*CEBPA*] and RUNX family transcription factor 1 [*RUNX1*]), although non-haematological manifestations further complicate some of these disorders. Mutations in these genes can also occur as acquired somatic mutations in myeloid neoplasms and confer prognostic significance for the affected individual, while not having implications for other family members. However, the presence of a mutation, identified on a somatic panel should always raise the suspicion of an occult germline predisposition. In this situation, differentiating somatic from germline mutations is vital.

Heritable predisposition to haematological malignancy may be suspected in affected individuals with a strong family history of associated haematological phenotypes, or in affected individuals with a personal history of other non-malignant syndromic features, but, as availability of genetic testing increases, so too does somewhat incidental identification of predisposing variants in individuals without a significant family history or obvious syndromic features.[1] The importance of identifying germline variants predisposing to haematological malignancy has been highlighted in recent European Leukaemia Net[2] and the United States National Comprehensive Cancer Network (NCCN) guidance[3] and is a mandated requirement in both the World Health Organization (WHO) 2022 classification[4–7] and International Consensus Classification of Myeloid Neoplasms.[8]

Genetic testing in the NHS

Molecular profiling of somatic and constitutional DNA in patients with haematological malignancy can either be done in a paired or unpaired, asynchronous manner (Figure 1). The unpaired route involves testing for an underlying germline

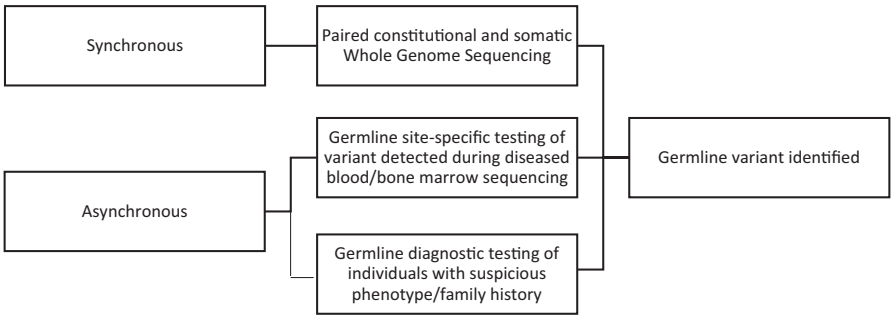

FIGURE 1 Approaches to somatic and constitutional DNA testing in haematological malignancy.

predisposition to haematological malignancy through intentional germline testing of individuals with a suspicious pedigree or clinical features, or, increasingly frequently, those inadvertently diagnosed with a potential germline variant by molecular profiling of diseased peripheral blood or bone marrow, termed somatic testing. Conversely, in recent times, paired, synchronous whole genome sequencing of constitutional and somatic DNA has become available as routine standard-of-care testing through NHS England for a host of different paediatric haematological malignancies, as well as for adult or paediatric onset acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL).[9] In the future, assessment for heritable predisposition to disease is likely to be undertaken routinely as part of the evaluation of many patients with haematological cancers through Specialised Integrated Haematological Malignancy Diagnostic Services[10] or similar services internationally.

Implications of hereditary predisposition to haematological malignancy for allogeneic BMT

Consideration of heritable predisposition to haematological malignancy is especially relevant for decision-making in allogeneic BMT, which is a cornerstone of therapy in many haematological cancers across all ages. There is frequently a clinical urgency to establish or refute a germline cause for the patient's underlying haematological malignancy. Often this needs to be done quickly following patient's initial clinical and diagnostic assessment. This is in order that donor searches are co-ordinated efficiently in tandem with remission induction or other treatments, ultimately followed by the delivery of transplant in a timely manner, when the disease status and general fitness for transplant have been optimised.[11]

Bone marrow transplantation is a relatively high-risk treatment, where choosing a suitable haematopoietic stem cell (HSC) donor is crucial for optimising outcomes. Options for potential donors include family members, either HLA-matched siblings, who, if present, are generally prioritised as donors, or, increasingly, haploidentical relatives, and any of these could be carriers. Alternatives to using family members are unrelated donors, listed on national or international registries and cord blood banks. Even here, there is need for caution, as there is some evidence from donor-derived leukaemia (DDL) rates that variants in genes associated with germline predisposition may be over-represented in cord blood transplants,[12,13] while one significant motivator to enrol in unrelated donor registries is the presence of leukaemia in a family member. These risks are primarily mitigated by using questionnaires as universal screening for germline predisposition syndromes is not available for volunteer unrelated donors. However, in the future, given the availability of high-throughput HLA-typing and sequencing, the feasibility of screening for germline predisposition may be explored, particularly as the safety of mobilisation using granulocyte colony-stimulating factor in the context of an occult germline mutation is unknown.

There are unique issues for both patient and potential donors when a germline predisposition is identified. For the patient there is a risk of DDL and the fact that certain germline variants are associated with non-malignant phenotypes (e.g., thrombocytopenia [*RUNX1*], lymphoedema and respiratory disease [*GATA2*], autoimmune disease [*DDX41*]),[4] which often have implications peri-transplant and for long-term follow-up. Although rare, DDL is a specific concern for the patient if they receive HSC donation from a related donor with a germline predisposition.[14,15] A recent survey from the European Society for Blood and Marrow Transplantation (EBMT) estimated a DDL prevalence of 80.5 cases per 100 000 transplants and a cumulative incidence at 5, 10, and 25 years after HSC transplantation of 0.067%, 0.132%, and 0.363% respectively, although this is likely to be an underestimate as, historically lack of awareness has almost certainly led to under reporting. Some studies have also suggested that when affected family members are used as donors, the likelihood of de novo leukaemia appears to be increased in the recipient compared to the donor, suggesting that the microenvironment and cytokine milieu in the recipient can drive the process.[16,17]

Equally importantly, identification of a germline predisposition to haematological malignancy has significant ramifications for the at-risk relative beyond deciding their suitability as a donor. If a germline variant is identified in the proband (most commonly the patient presenting with haematological cancer in this context), then there are various implications for potential family donors. These include the need for testing for the possibility of a frightening new 'diagnosis', complicated by the lack of comprehensive information on disease penetrance and the natural history of these conditions, further compounded by lack of consensus regarding best practice for surveillance of asymptomatic carriers of pathogenic variants.

Issues with variant classification, germline confirmatory testing, and predictive testing in at-risk relatives (potential donors)

Constitutional pathogenic variants in six genes (*DDX41, ETV6, CEBPA, RUNX1, ANKRD26* and *GATA2*) are known to significantly increase the risk of haematological malignancy, and several other candidate genes have been identified but are less well characterised. Interpretation and classification of variants in these genes is challenging given the relative paucity of functional data, case–control analyses, and phenotypic specificity. There is a need for gene-specific guidance. Indeed, modifications of current classification guidelines for *RUNX1*[18] have recently been developed and similar guidance for other genes will follow as more information becomes available.

Variants in any gene can be classified by their likely pathogenicity and these are shown in Table 1.[19–23] Under most circumstances only Class 4 or 5 variants (P/LP) will trigger further investigation. Variants of uncertain significance (VUS)

TABLE 1 Classification of variants in genes that predispose to haematological malignancy showing resultant reporting and testing strategies.

Variant class			Probability of pathogenicity, %	Reported if identified in somatic-only context	Reported if identified in germline context	Predictive testing offered to at-risk unaffected relatives
5	Pathogenic		>99	Yes	Yes	Yes
4	Likely pathogenic		90–99	Yes	Yes	Yes
3	Variant of uncertain Significance	Hot	81.2–90	Depending on discussion at GTAB	Yes	Depending on discussion at GTAB
		Warm	67.5–81.2	Depending on discussion at GTAB	Yes	Depending on discussion at GTAB
		Tepid	50–67.5	No	No	No
		Cool	32.5–50	No	No	No
		Cold	18.8–32.5	No	No	No
		Ice cold	10–18.8	No	No	No
2	Likely benign		0.1–10	No	No	No
1	Benign		<0.1	No	No	No

Abbreviation: GTAB, Genomic Tumour Advisory Board.

are frequently identified and may sometimes cause problems in patient management because of uncertainty about their clinical relevance. In addition, because the approach to interpretation, classification and reporting of variants identified in the somatic context may be different to that of variants of germline origin,[23] discordance between classification of variants detected during tumour-focussed testing and confirmatory germline testing may arise. Identification of VUS of likely germline origin poses a challenge for so-called 'somatic' testing laboratories given that many somatic laboratories do not routinely report VUS unless management would be impacted.

In general, germline VUS are not considered clinically actionable (Table 1),[24] and site-specific testing of unaffected at-risk relatives for familial VUS is not generally recommended. In addition, if a VUS of suspected germline origin is identified on somatic profiling of diseased blood/bone marrow in an individual with a haematological malignancy, confirmatory germline testing would not ordinarily be recommended. However, there may be rare cases, where the weight of available evidence suggests that a VUS of suspected germline origin is more likely to be pathogenic than benign, e.g., in the context of a very strong family history. Here, reporting and germline confirmation of the finding may be beneficial, particularly if allogeneic BMT is a consideration, and if carrier status of at-risk relatives would impact donor selection. These cases require discussion at a specialist multidisciplinary team (MDT) meeting.[25]

The UK Clinical Genetics Group (UKCGG), CanGene-CanVar and the NHS England Genomic Laboratory Hub (GLH) Haematological Oncology Malignancies Working Group consensus meeting

A multitude of clinical challenges specifically related to patients with confirmed/suspected heritable predisposition to haematological malignancy were recognised by clinicians across multiple specialties. These included to whom genetic testing should be offered, when this should occur, what form this should take, what sample type should be used for constitutional DNA analysis in affected individuals, as well as which clinicians should perform pre-test genetic counselling in affected individuals or at-risk relatives. These challenges, and a relative paucity of national/international best practice guidance related to such issues prompted a number of key stakeholder groups (the UKCGG [a constituent group of the British Society of Genomic Medicine], the Cancer Research UK (CRUK)-funded CanGene-CanVar Programme, and the NHS England GLH Haematological Oncology Malignancies Working Group) to establish a virtual workshop involving patient representatives and key experts in Clinical Genetics, Genetic Counselling, Haematology and Nursing from across the UK in April 2022.

A detailed report of the outcome of this workshop and consensus reached in relation to ethical, laboratory and clinical aspects of management and surveillance of patients and carrier relatives is set out in detail in a companion manuscript.[25] Readers are referred to this for a detailed discussion of variant classification of somatic and germline variants, pathways and sample selection for confirmatory genetic testing, informed choice and consent for confirmatory and pre-symptomatic genetic testing, and surveillance of unaffected carriers.

During the discussions at this initial meeting, it became apparent that the identification of P/LP Class 4 and 5 variants of germline origin in an individual being considered for an allogeneic BMT from a family donor (either fully matched or haploidentical) creates a unique set of challenges for managing the patient and potential donor. Donor-selection algorithms are complex and inevitably depend on a multiplicity of patient and donor factors that are frequently impacted by turnaround times (TATs) of testing and reporting. Alongside the choice of donor must be balanced the risks of alternative non-transplant treatment pathways. The MDT meeting, often working closely with Specialist Integrated

Haematological Malignancy Diagnostic Services (SIHMDS) and Histocompatibility and Immunogenetics (H&I) laboratory staff, are key to co-ordinating the information exchange and making the best decisions in a timely manner. Therefore, it was decided to convene a specific workshop to reach consensus on issues relating to BMT, the outcomes of which are described here.

METHODS

The recommendations in the present consensus guideline were developed following a virtual workshop held in July 2022 dedicated to discussing the impact of germline predisposition to haematological malignancies on specific issues related to allogeneic BMT. The methodology for the Transplant-Specific Workshop was similar to that employed previously in the initial consensus meeting convened by UKCGG, CanGene-CanVar and the NHS England GLH Haematological Malignancies Working Group.[25]

The final consensus recommendations were developed using

1. In-meeting polling to address targeted questions. Using this approach, all meeting attendees were involved in reaching this consensus in real time (Table 2).
2. In-meeting discussion following polling. Several areas triggered significant discussion amongst participants.

TABLE 2 Statements on which consensus was reached.

1. *Patients requiring BMT should be assessed for potential heritable cause for their phenotype including clinical examination, family history assessment, review of somatic genetic variants and germline testing according to National Genomic Test Directory* (*n* = 55 respondents). (Agree/strongly agree 100%)
2. *Where there are concerns about possible/confirmed heritable risk, unrelated volunteer donor (VUD) search and confirmatory testing of selected VUD should happen in parallel with evaluation of related donors to allow donor options to be assessed without delay* (*n* = 52 respondents). (Agree/Strongly agree 92%)
3. *If concerned about a strong family history/syndromic features in the absence of a confirmed genetic diagnosis, it would be best practice to discuss in the MDT to document the history and decide whether related donors would be prioritised above unrelated donors* (*n* = 52 respondents). (Agree/strongly agree 94%)
4. *If concerned about a strong family history/syndromic features, the family should be referred to clinical genetics service for further advice and management* (*n* = 56 respondents). (Agree/ strongly agree 100%)
5. *If a P/LP (Class 4/5) variant is identified in the proband which is/is likely to be germline and causative of phenotype, putative donor relatives should be offered urgent access to genetic counselling with regards to their own options for testing and outcomes* (*n* = 52 respondents). (Agree/ strongly agree 96%)
6. *If a VUS (Class 3) is identified in the proband which is/is likely to be germline and possibly causative, whether this is actionable for BMT pathways should be discussed/documented in an MDT including germline scientists, haematology, and genetics* (*n* = 48 respondents). (Agree/strongly agree 89%)
7. *If an MDT decision is made to undertake testing for an uncertain Class 3 variant to inform BMT pathways, relatives should be offered genetic counselling by clinical genetics to ensure they understand the uncertainty and outcomes of testing* (*n* = 48 respondents). (Agree/strongly agree 94%)
8. Potential donor relatives should be aware that they have the option to decline germline genetic testing in the acute setting and offered expert advice to enable them to make an informed decision on the timing of their own genetic test result (*n* = 51 respondents). (Agree/ strongly agree 100%)
9. *Germline testing of potential donors in an urgent situation can proceed in parallel with confirmatory testing in the patient; however, potential donors should be informed of the fact germline confirmation in the proband has not yet occurred* (*n* = 45 respondents). (Agree/strongly agree 83%)
10. *Where the predictive testing of a germline variant in potential donor relatives has been undertaken urgently, to inform BMT decisions, matched relatives shown NOT to carry the variant would usually be prioritised over matched carrier relatives* (*n* = 48 respondents). (Agree/ strongly agree 87%)
11. *Where predictive testing of a germline variant in potential donor relatives has been undertaken urgently to inform BMT decisions, a relative shown to be a carrier would not usually be considered as a potential donor unless other options were limited* (*n* = 43 respondents). (Agree/ strongly agree 93%)
12. *Where all related matched donors are carriers, careful assessment of risks and benefits of an unrelated donor versus a carrier family member requires discussion at a MDT meeting with access to expert opinion and consideration on a gene specific basis* (*n* = 43 respondents). (Agree/ strongly agree 98%)
13. *When a matched relative declines testing, careful assessment of risks and benefits of an unrelated donor versus a untested family member requires discussion at a MDT meeting with access to expert opinion and consideration on a gene specific basis* (*n* = 44 respondents). (Agree/ strongly agree 95%)
14. *Potential donor relatives who test positive for the familial genetic variant should be offered a rapid post results follow-up appointment with an expert in genetic counselling who can provide both clinical and psychosocial support* (*n* = 40 respondents). (Agree/ strongly agree 93%)

These discussions were also informed by state-of-the-art presentations on the day, recorded and subsequently collated. They complimented the in-meeting polling and helped frame the resultant recommendations.
3. Finally, recommendations are included for practically achieving the targeted consensus statements.

Individual recommendations carry superscript numbering to reflect these sources. Full in-meeting polling results are listed in Table 2.

Pre-meeting preparation

An organising committee of six clinicians comprising adult and paediatric haematologists specialising in BMT, Clinical Geneticists with specialist interest in haemato-oncology, and a haematologist with specialist interest in hereditary haematological malignancy was established. Within the committee, there was representation from four national collaborative groups; the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT),[26] UKCGG,[27] the CRUK-funded CanGene-CanVar research programme (CGCV)[28] and the NHS England GLH Haematological Malignancies Working Group.

Invitations to attend a short, focussed, virtual workshop were sent to attendees of the preceding consensus meeting, along with additional key stakeholders and clinicians with specialist expertise in bone marrow transplantation. Relevant background information, and a link to the recording of the previous consensus meeting (https://www.ukcgg.org/information-education/ukcgg-consensus-meetings/) were sent to all registered participants.

The organising committee collaboratively generated and refined a set of statements upon which to gather consensus by in-meeting polling during the workshop based on their collective areas of expertise.

Workshop format

The process followed in the preceding consensus workshop[21] was recapitulated with a focus on allogeneic BMT, particularly focussing on the impact on donor selection. The meeting comprised a series of talks from members of the organising committee, with a summary of the key outputs of the previous consensus workshop, followed by overviews providing state-of-the-art information relating to germline predisposition in haemato-oncology in paediatrics and adults, with a focus on the impact of the evolving information and evidence on allogeneic BMT and donor-selection practice. Thereafter, a number of polls were conducted, determining strength of agreement on statements for best practice in different scenarios as previously agreed by the core committee. Following each talk, and throughout the poll, attendees were invited to comment on the issues raised, which generated discussion and debate. A threshold of ≥80% of respondents selecting 'agree'/'strongly agree' was taken as consensus agreement for a particular statement. Given the multidisciplinary nature of the audience, not every participant was expected to respond to every statement, but a quorum of at least 40 respondents was required for consensus to be considered valid. If consensus on a particular statement was not reached, the statement was debated and rephrased in line with suggestions from the audience until such a time that consensus could be agreed, if at all.

RESULTS

Participants

A full list of participants is given in Appendix S1. The meeting demographics included wide representation from all stakeholders in this area. There were 16 Clinical Geneticists, eight Paediatric consultant haematologists, 17 Clinical Scientists (14 somatic, three somatic and germline), 23 adult haematologists/BMT consultants, six Genetic Counsellors, one Clinical Nurse Specialist and three researchers. Eight participants did not complete full affiliations. Of the 82 participants 66 participated in the in-meeting polling.

In-meeting polls

Consensus was achieved on 14 of 16 statements regarding various clinical scenarios. The results are summarised in Table 2.

CONSENSUS RECOMMENDATIONS

A dedicated pan-UK meeting brought together a focussed group of stakeholders to discuss and reach consensus on how to manage challenges unique to BMT, in individuals with confirmed or suspected hereditary predisposition to haematological malignancies, particularly in relation to testing and selection of related donors, balancing the urgent needs of the affected patient against the potential impact of testing on at-risk asymptomatic relatives.

At present this is a relatively rare situation. However, rapid expansion of high-throughput sequencing into standard care will lead to more frequent identification of individuals with germline variants in genes known to be associated with haematological cancer, as well as identify VUSs and variants in genes hitherto unknown to be associated with such predisposition ('genes of uncertain significance') in families with a suggestive history.[4] Currently, there is almost no guidance in this area. The 2022 European Leukaemia Net AML guidelines recommend testing for germline risk alleles early in management but highlight the lack of data on most variants except those in *RUNX1* and *CEBPA*.[2] The 2022 British Society for Haematology (BSH) good practice recommendations for laboratory testing in AML stress the

identification of familial predisposition to haematological malignancy enabling referral to clinical genetics and wider testing when considering a related-donor allogeneic transplant but do not include details on donor selection.[29]

Recommendations reflect consensus obtained from in-meeting polling and subsequent discussion combined with practical guidance to achieve these consensus aims. For clarity each recommendation is mapped to in-meeting polling,[1] in meeting discussion[2] or post-meeting practical considerations.[3]

Need for awareness, education, training, and access to expertise

There was discussion around the rapidity with which this field is moving. While there has been an exponential increase in the awareness and understanding of these conditions amongst treating haematologists and other transplant clinicians, it is still possible that patients may be referred for allogeneic BMT either undiagnosed or without full evaluation for these syndromes and the transplant team need to develop a high level of clinical suspicion. The need for education and guidance to be produced describing these genes and their clinical significance, to inform healthcare professionals working in transplant was recognised. Establishing local multidisciplinary and multispecialty working practices and the need to develop pathways to manage these patients was seen to be essential. A clear desire was expressed for local laboratories and transplant teams to be able to access guidance from national experts on specific genes.

Recommendations

- *Patients requiring BMT should be assessed for a potential heritable cause for their phenotype including clinical examination, family history assessment, review of somatic genetic variants and germline testing according to National Genomic Test Directory.*[1]
- *Access to an MDT with experience in the management of transplant patients and their relatives who have a germline predisposition to haematological malignancy, especially with regard to initial diagnosis and choice of suitable donors for transplant, should be established.*[2]
- *Education materials and programmes should be designed to raise awareness of germline predisposition to haematological malignancies as they affect allogeneic BMT.*[2,3]
- *Clear local pathways for the management of BMT patients with a germline predisposition, and their relatives, should be established.*[3]

Urgency and timescales

For patients being considered for BMT, the desired time from variant identification to transplant is relatively short compared to current timescales for genetic counselling, testing, and reporting. Where a variant of suspected germline origin is identified through somatic testing, there is an urgency to perform confirmatory germline testing on a representative sample of constitutional DNA. A hierarchy of potential germline samples is listed in the consensus guidelines from the initial meeting.[25] Peripheral blood can be used to screen relatives who are not currently expressing a disease phenotype. TATs may be further impacted by variant complexity, or if there are queries regarding pathogenicity or actionability of a variant that require multidisciplinary input. Once it has been agreed that germline testing is indicated, and where germline status has been confirmed, there is then further urgency in testing of potential related donors for the familial variant, possibly simultaneously with tissue typing. Considering these time pressures there may be occasions where cascade testing in at-risk relatives happens contemporaneously with, or even prior to, confirmatory germline testing in the affected patient.

Recommendations

- *Where germline status in a patient has already been confirmed, testing of potential related donors for the variant may occur simultaneously with tissue typing.*[2,3]
- *Where there are concerns about possible or confirmed heritable risk, VUD search and confirmatory testing of selected VUD should happen in parallel with evaluation of related donors to allow donor options to be assessed without delay.*[1]
- *Germline testing of potential donors in an urgent situation can proceed in parallel with confirmatory testing in the patient; however, potential donors should be informed of the fact germline confirmation in the proband has not yet occurred.*[1]

Donor selection

It was appreciated that all efforts should be made to avoid inadvertently selecting a donor who carries a germline variant predisposing to a haematological malignancy. There was discussion around the fact that DDL is a rare complication of allogeneic BMT but that the true risk is likely to be higher than that published in the literature and that this risk was likely to be increased further in those receiving a graft from an affected family member. While every effort should normally be made to avoid using a carrier family member as a donor there may be situations where this is unavoidable, or uncertainty remains, for instance if a potential familial donor declines site-specific testing for the familial variant, or if the variant identified in the proband is of uncertain significance. It was acknowledged that there may be occasions where donor options for the patient are so poor that the risk–benefit ratio is in favour of using an unaffected carrier as a donor to allow the patient to receive a potentially life-saving transplant procedure.

Recommendations

- *It is important to avoid inadvertently using a carrier relative as a donor. This requires a high index of suspicion, and appropriate, timely, targeted testing of patients and their potential family donors.*[2,3]
- *Where the predictive testing of a germline variant in potential donor relatives has been undertaken urgently to inform BMT decisions, matched relatives shown NOT to carry the variant would usually be prioritised over matched carrier relatives.*[1]
- *Where predictive testing of a germline variant in potential donor relatives has been undertaken urgently to inform BMT decisions, a relative shown to be a carrier would not usually be considered as a potential donor unless other options were limited.*[1]
- *If concerned about a strong family history/syndromic features in the absence of a confirmed genetic diagnosis, it would be best practice to discuss in the MDT meeting to document the history and decide whether related donors should be prioritised above unrelated donors.*[1]
- *Where all related matched donors are either carriers or decline testing, careful assessment of risks and benefits of an unrelated donor* versus *a carrier family member/untested family member requires discussion at a MDT meeting with access to expert opinion and consideration on a gene-specific basis.*[1]

Genetic counselling

There was consensus on the need for genetic counselling to enable potential donors to understand their choices around predictive genetic testing and the implications results would have for their own risk beyond their selection as donor for their affected relative. There was discussion about the extent to which this should be provided by genetic counsellors and to what extent it could be provided by the transplant MDT, who would need support with appropriate education and written information for potential donors. In practical terms, it is likely that currently the demand for urgent genetic counselling outstrips availability in most centres and local arrangements may need to be put in place whereby haematologists perform some of these tasks, with support from local Clinical Genetics services. However, planning for dedicated, skilled counselling in this area should remain the aim. One important aspect to consider in BMT, which is underpinned by the Joint Accreditation Committee International Society for Cell and Gene Therapy (ISCT)-Europe and EBMT (JACIE) accreditation standards and in the case of donors without capacity (including minors), by Human Tissue Act (HTA) regulation, is separation of the clinical care of HSC donors from that of the recipient, which enables independent advocacy and avoids conflict of interest, so that no undue pressure is placed on relatives to donate and that a decision to donate, or not, is without prejudice. In some circumstances this may mean that donor medical teams may be best placed to counsel, but specialist education and training will be required. Alternatively, counselling may be performed by haematologists and/or other trained specialists external to the BMT programme.

Recommendations

- *Dedicated, skilled genetic counselling in this area remains the 'gold standard' and this should become an essential component of future integrated haematological oncology service design.*[2,3]
- *The essential separation of the clinical care of donors from that of the recipient, which enables independent advocacy and avoids conflict of interest, so that no undue pressure is placed on relatives to donate and ensures that a decision to donate, or not, is without prejudice should be maintained at all times.*[3]
- *If local clinical genetic services are unable to provide counselling, then the donor medical teams may be best placed to counsel, but specialist education and training will be required. Alternatively, counselling may be performed by haematologists and/or other trained specialists external to the BMT programme.*[3]
- *If concerned about a strong family history/syndromic features, but without a P/LP variant the family should be referred to clinical genetics service for further advice and management.*[1]
- *If a P/LP (Class 4/5) variant is identified in the proband which is/is likely to be germline and causative of phenotype, putative donor relatives should be offered urgent access to genetic counselling with regards to their own options for testing and outcomes.*[1]
- *Potential donor relatives should be aware that they have the option to decline germline genetic testing in the acute setting and offered exert advice to enable them to make an informed decision on the timing of their own genetic test result.*[1]
- *Potential donor relatives who test positive for the familial genetic variant should be offered a rapid post result follow-up appointment with an expert in genetic counselling who can provide both clinical and psychosocial support.*[1]

Considering VUS

The topic of germline VUS in genes predisposing to haematological malignancy generated considerable discussion. On the one hand, using a related donor with a variant that is in fact disease-causing exposes the recipient to the risk of DDL. Conversely, rejecting a related donor with a VUS that is in fact benign risks potentially inappropriately selecting a less-optimal donor. There is variability between Genomic Tumour Advisory Boards (GTABs) on whether VUS are included in final genetics reports in patients with haematological cancer, and moving forwards, national standardisation, co-ordination, collection and analysis of this data is warranted to evaluate their significance.[25] The identification of a VUS in a transplant patient will not usually impact on patient or relative management or donor selection (Table 1). In rare cases where the clinical suspicion

of a germline predisposition is very high, expert discussion at a specialist MDT meeting will be required. This meeting will take all clinical factors into consideration, combined with somatic and germline variant interpretation, using gene-specific guidance, where available. The local GTAB may also determine if a VUS is actionable for purpose of donor exclusion, if highly suspicious and in a high-risk gene when no non-inferior unrelated donor option is a possibility.

Recommendations

- *When a Class 3 VUS is identified then further assessment of clinical status and family history is warranted to inform MDT discussions.*[1]
- *If a MDT decision is made to undertake testing for an uncertain Class 3 variant to inform BMT pathways, relatives should be offered genetic counselling by clinical genetics to ensure they understand the uncertainty and outcomes of testing.*[1]

Data collection of DDL, graft failure and other adverse events

In addition to gathering data on VUS, above, there was discussion of the need for national collection of data on DDL and graft failure, especially in situations when a relative with a P/LP variant has been used as a donor.

Recommendation

- *A national database should be established to collect data on DDL and graft failure rates when carriers known to be affected with the mutation are used as donors.*[2]

Involvement of patients and relatives

The original meeting on germline predisposition included patient representatives.[21] Amongst participants in this meeting, no-one identified as a patient representative.

Recommendation

- *It is imperative that the views and experiences of individuals with haematological malignancy with germline predisposition having allogeneic transplant, and relatives who either undergo or decline testing as potential donors are sought in future.*[2]

Resources

All developments require allocation of human and financial resource, as well as training and education of existing individuals in Clinical Genetics, Haematology/BMT and Clinical Scientific and Biomedical Staff in associated laboratories, which not only are required to take on additional testing for new tests and greater numbers of tests from patients and families, but also consider the rapidity of TATs and, in conjunction, the clinical processes for evaluation, counselling, and donor clearance services.

Recommendation

- *Scoping of future Haematological Oncology, Transplant and Genetics services should include resource allocation for diagnostic testing for germline predisposition to haematological cancer and genetic counselling services.*[3]

Future collaborative research

This group of multidisciplinary specialists plan to continue our collaborative efforts to address issues highlighted by this and preceding consensus meetings, taking advantage of the unique features of the integrated NHS and Genomic Medicine Service to inform best practice for this group of patients across the UK.[25]

AUTHOR CONTRIBUTIONS

Andrew Clark, Terri P. McVeigh, Katie Snape, Austin Kulasekararaj, Jacob Grinfeld, John A. Snowden were part of the organising committee and contributed significantly to the planning, delivery and manuscript preparation. John A. Snowden, Andrew Clark, Katie Snape and Terri P. McVeigh: responsible for conceptualisation, organisation of meeting, oversight of process and review of manuscript. Andrew Clark, Sally Thomas: writing first draft and editing with co-author comments. Andrew Clark, Sally Thomas, Angela Hamblin, Polly Talley, Austin Kulasekararaj, Jacob Grinfeld, Beverley Speight, Katie Snape, Terri P. McVeigh: contributed to meeting, reviewed the initial manuscript, and approved the final version for submission.

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CONFLICT OF INTEREST STATEMENT

No conflicting/competing interests declared.

DATA AVAILABILITY STATEMENT

All data are contained within the paper. No other data are available, except the participant list found in the supplementary information for this journal article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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