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GUIDELINE

Germline predisposition to haematological malignancies: Best practice consensus guidelines from the UK Cancer Genetics Group (UKCGG), CanGene-CanVar and the NHS England Haematological Oncology Working Group

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Summary

The implementation of whole genome sequencing and large somatic gene panels in haematological malignancies is identifying an increasing number of individuals with either potential or confirmed germline predisposition to haematological malignancy. There are currently no national or international best practice guidelines with respect to management of carriers of such variants or of their at-risk relatives. To address this gap, the UK Cancer Genetics Group (UKCGG), CanGene-CanVar and the NHS England Haematological Oncology Working Group held a workshop over two days on 28–29th April 2022, with the aim of establishing consensus guidelines on relevant clinical and laboratory pathways. The workshop focussed on the management of disease-causing germline variation in the following genes: *DDX41*,

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CEBPA, *RUNX1*, *ANKRD26*, *ETV6*, *GATA2*. Using a pre-workshop survey followed by structured discussion and in-meeting polling, we achieved consensus for UK best practice in several areas. In particular, high consensus was achieved on issues regarding standardised reporting, variant classification, multidisciplinary team working and patient support. The best practice recommendations from this meeting may be applicable to an expanding number of other genes in this setting.

KEYWORDS
clinical pathways, germline predisposition, haematological malignancy, leukaemia, transplant, variant classification

BACKGROUND

Next-generation sequencing (NGS) is now standard of care in the diagnostic evaluation of patients with suspected haematological malignancies. Within NHS England (NHSE), eligibility for testing is laid out by the Genomic Test Directory.[1] The identification of somatic gene variants can inform diagnosis, prognosis and therapeutic options. Tumour-based (bone marrow or leukaemic blood cells) testing using multigene panels or paired tumour and germline whole genome sequencing (WGS) can also identify individuals with potential or confirmed germline predisposition to haematological malignancy. Identifying these patients and establishing pathways for appropriate germline confirmation with the possibility of cascade predictive testing in family members is a relatively new area of expanding clinical and laboratory work. Key challenges identified early on within clinical practice include decisions on which genes and variants should be analysed and/or reported, appropriate sample types for testing, clinical pathways and management of gene variant carriers.

From somatic detection to germline confirmation

In UK practice, detection of a germline variant after paired tumour and germline WGS would be included on the report for discussion with the patient, in line with the preceding informed consent. Detection of a somatic variant that is suspicious of being in the germline raises more questions regarding what and how to include on the report and similar questions arise from both situations regarding the downstream clinical and patient pathways.

In UK clinical practice, analysis of assumed malignancy-derived variants identified during analysis of somatic tissue usually leads to the classification of variants as being associated driver variants (oncogenic), uncertain variants or variants that are not relevant to the oncogenic process. This classification process is slightly different to the process of classification of the same variants when identified in the germline setting. Germline classification is performed according to the American College of Medical Genetics and Genomics (ACMG) variant interpretation guidelines.[2] This classifies variants as 'Benign' (Class 1), 'Likely Benign' (Class 2), 'Variants of Uncertain Significance' (VUS) (Class 3), 'Likely Pathogenic' (Class 4) and 'Pathogenic' (Class 5). There are no definitive guidelines about when to proceed to germline testing after somatic panel testing for haematological malignancy when synchronous, paired testing is not available. A suggested workflow was published following a review of current practice in the UK, Australia and the USA.[3] Germline VUS are generally not considered clinically actionable and in line with Association for Clinical Genomic Science (ACGS) recommendations, they are not typically reported,[4] with the exception of rare cases when further investigations may provide additional evidence to upgrade them to likely pathogenic.

In 2019, the European Society for Medical Oncology (ESMO) Precision Medicine Working Group sought to generate guidelines on germline-focussed analysis of tumour sequencing data, indications for germline testing and patient information/consent. Their published recommendations were based on the somatic–germline conversion rate in paired sequencing data from >16 000 solid cancers.[5] In summary, these guidelines advise that germline focussed analysis should be offered where a variant is predicted to be likely pathogenic/pathogenic in the germline setting, highly penetrant and found at a variant allele frequency (VAF) of >30% for single nucleotide variants or >20% for small insertions or deletions. Caution was advised regarding variants in genes that are not proven through research to be of high penetrance, or variants in genes associated with disorders unrelated to the malignancy for which testing was undertaken ('off-tumour').

Using a set threshold for when to consider the potential of a variant identified on a somatic panel to also be present in germline has limitations, including overlooking variants at lower VAF due to poor coverage or copy number variation/loss of heterozygosity (LOH).[6] In the Li et al.[6] (2020) position statement from the ACMG, which considers the potential for detection of germline variants following tumour testing, the authors recommended counselling and consent for the possibility of revealing an inherited causal variant before somatic testing and highlighted the potential for fluctuations in VAF due to LOH. Of note, there can sometimes still be a role for germline testing in the absence of a variant found on somatic testing (e.g., due to loss of the germline variant in the tumour cells in emergent subclones). Somatic panel testing may fail to identify

copy number variants and large exon-spanning deletions, which can be found using the alternative methods of WGS or SNP arrays.

Research evidence on patient preferences indicates that most patients with cancer would prefer to know of incidental germline findings irrespective of whether the associated condition is preventable.[7] Qualitative research evidence from focus groups including both patients with cancer and the general public suggests that the option of receiving additional information and secondary findings from genomic testing should be given by health professionals, with the decision on whether to know and how the information is shared to remain with the patient.[8] Health professional feedback about the utility and management of secondary findings in genomic medicine upheld the importance of patient choice, whilst also urging caution in disclosure without a strong evidence base about the impact and potential harms.[9]

Sample types for germline testing

In contrast to solid tumours, in the setting of haematological malignancy, blood and saliva are unsuitable samples due to the predominance of tumour DNA. Sample options in this setting are a skin biopsy or remission bone marrow sample. T-cell purified DNA sample from blood, buccal scrapes and bone marrow-derived stroma cells can also be used, although they are not currently eligible samples according to the Genomic Test Directory.[1] A summary of some advantages and disadvantages of these is shown in Table 1. Other samples such as urine, fingernails and skin swabs have been shown to yield insufficient DNA for testing,[10] and many UK laboratories are not set up for DNA extraction from these samples.

Consent in germline testing pathways

The ESMO guidelines acknowledged that consent and sample storage for possible germline confirmation can be included ahead of somatic panel NGS, but is often a more staged approach, occurring after variant review and classification. The more recent ACMG guidance advises more strongly that patients should be informed of the potential to reveal an inherited predisposition in advance of arranging diagnostic somatic panel testing, with some suggested wording for clinicians.[5] Irrespective of timing, information provision and documented consent is conventional practice and a requirement prior to germline confirmatory testing. There has been a general move towards mainstream germline testing in the solid cancer setting, with a referral for genetic counselling following confirmation of a germline pathogenic variant.[11] Survey-based qualitative research evidence in a separate study of nearly 1000 patients with solid cancers showed high acceptability and satisfaction of a mainstream genetic testing model.[12] Suggested models of care in the haematological setting also reflect the need for patient information and

TABLE 1 Advantages/limitations of sample types available for germline confirmation in patients with haematological malignancies.

Sample type	Advantages	Disadvantages
Skin biopsy	High quantity DNA source Cell culture option to increase yield	• Invasive procedure • May not be possible in all centres • The requirement for culture to avoid contamination adds time delay • If uncultured, chance of contamination by leucocyte-derived DNA
T-cell sorting	Easily accessible sample (blood)	• Need specialist laboratory • Cannot be done in all centres • Possibility of early somatic haematopoietic mutations misdiagnosed as germline • Possibility of concomitant non-haematopoietic tumour mutations present in circulation • 'Gold standard' involves expensive fluorescence-activated cell sorting sorting otherwise risk of contamination
Buccal scrape	Easy access sample Patients can self-sample at home	• Contamination by leucocyte-derived DNA[a]
Hair root	Easy access sample Patients can self-sample at home	• May not yield enough DNA • Not all laboratories set up for extraction from these samples • Possibility of contamination of DNA from other sources
Nail clipping	Easy access sample Patients can self-sample at home	• May not yield enough DNA • Few laboratories set up for extraction from these samples • Possibility of contamination of DNA from other sources
Remission sample (bone marrow aspirate or remission blood)	Reduces the number of samples needing germline confirmation Avoids the requirement of more invasive separate sampling, e.g., skin biopsy	• May delay germline confirmation • Remission sampling may not give a clear result • Not all patients have remission bone marrow sampling • May not be suitable in urgent cases • Possibility of residual clonal somatic haematopoietic mutations misdiagnosed as germline

[a]Shown to be low if procedure optimised for epithelial cell recovery.[10]

informed consent at various stages, with a requirement for formal genetic counselling around confirmation of a germline pathogenic variant[13–15] and, by extension, at the time of predictive testing in their family members.

Donor selection

If the treatment of haematological malignancy is to involve allogeneic haematopoietic stem cell transplantation, donor selection warrants consideration of any potential germline predisposition.[13] If an asymptomatic related donor is being considered, predictive testing for the known variant should be offered. Donor-derived leukaemias after transplant from a relative who was a carrier of a familial germline pathogenic variant have been reported for *DDX41*,[16] *GATA2*[17] and *RUNX1*.[18] Consideration of how predictive testing may inform bone marrow donor selection, whilst upholding a relative's right not to know would normally be addressed in a genetic counselling consultation.

METHODS

Pre-meeting preparation

The organising committee comprised of six health professionals representing haematology, clinical genetics, genetic counselling and clinical scientists, from three national collaborative groups, the UK Cancer Genetics Group (UKCGG),[19] the Cancer Research UK (CRUK) funded CanGene-CanVar research programme (CGCV)[20] and the NHSE Haematological Oncology Working Group.[21] The organising committee worked in different regions of England and Scotland. Six genes, *DDX41*, *CEBPA, RUNX1*, *ANKRD26*, *ETV6* and *GATA2*, were chosen as the focus of this meeting based on the organising committee's experience in clinical practice regarding germline questions after somatic (tumour-only) gene panel testing, as well as the existence of some research evidence that could form the basis of potential consensus decisions. Extensive review of the literature and clinical characteristics, genetics and prevalence of established inherited predisposition to haematological malignancy syndromes was undertaken[22–46] and used to develop a background document for delegates.

Invitations were sent to each Genomics Laboratory Hub (GLH) within NHSE, plus the Regional Genetics Services in Scotland, Northern Ireland and Wales, alongside clinical haematological services in each GLH region and policy-makers from NHSE. Representatives from the following specialities were encouraged to register: Haematology, Clinical Genetics, Clinical Scientists, policy-makers and patient representatives.

Prior to the meeting, the background document and a scoping survey (Appendix S3 for the survey questions) were sent out to registered delegates. This approach has been successful for other UKCGG guidelines.[47] The survey questions aimed to assess current practice and to seek opinion on potential best practice pathways. The themes arising from the survey were then used to create a series of key questions to be addressed at the consensus meeting.

Consensus group participants

A total of 146 stakeholders registered to attend from across the UK, including patient support group representatives, clinical cancer geneticists, genetic counsellors, paediatric and adult haematologists and clinical scientists (somatic and germline). Each of the seven GLHs within NHSE were represented, as well as delegates from Scotland, Wales and Northern Ireland. Some colleagues from Republic of Ireland and the Netherlands were also invited as observers and to give an international perspective where appropriate. A list of consensus meeting attendees is provided in Appendix S1.

Workshop format

An outline and agenda for the meeting is available in Appendix S2. The first part of each meeting day involved a structured series of talks. These covered the survey results, somatic and germline variant interpretation, national infrastructure, penetrance and genetic considerations associated with the six genes, consent and cascade testing considerations. These presentations provided a review of the available evidence and equipped the delegates from a variety of backgrounds with up-to-date evidence on which to base their recommendations. Slides and some recordings from the day are available online at: https://www.ukcgg.org/information-education/ukcgg-consensus-meetings/.

Thereafter, a number of related polls were conducted, with proposed statements for best practice in different scenarios. Each poll was closed when at least half of delegates had submitted a response. In practice, this was a cut-off of 60 votes, as not all registered participants could attend in full on both days (participants on day 1 = 106, day 2 = 93), and in consideration that patient representatives, or those for whom specific scientific or clinical questions were outside of their area of expertise might abstain from voting. Consensus was deemed to be reached when ≥80% respondents selected 'Agree/Strongly Agree' or 'Yes' in response to the statement posed. Within the Delphi process it is important to set a consensus level at the beginning of the process.[48] If an argument was proposed requiring revision to the wording of the statement, this was undertaken in 'real-time' and the poll was repeated with the revised wording to generate a final decision.

Time was allocated for whole group discussion around each polling question for feedback, discussion and debate, which helped inform any consensus reached. After the meeting a summary was posted on the UKCGG website: https://www.ukcgg.org/information-education/ukcgg-consensus-meetings/.

RESULTS

The response rate to the pre-meeting survey was 61/146 (42%). A total of 21 (34%) responders were Clinical Scientists, with a focus on germline only (n = 4), somatic only (n = 11) or both germline and somatic (n = 6). The other responders were from Clinical Haematology (n = 9), Clinical Genetics (Consultants n = 18, Genetic Counsellors n = 3) and a smaller number from the research/academic sector (n = 4). A total of five patient representatives responded to the pre-meeting survey. One responder did not provide their role. Responses were included from all GLHs in England, Scotland and Wales. Although pre-survey responses were not obtained from clinicians or scientists in Northern Ireland, participants from this region were included in the consensus meeting.

Results from the pre-meeting survey demonstrated that current practice involves somatic panels that include genes with potential germline predisposition. In current somatic panels, the most common genes in this category were *DDX41, CEBPA, RUNX1, ETV6, GATA2* as well as *ANKRD26*, with some variation between different services.

The statements on which consensus was reached as best practice guidelines are summarised in Table 2. Further comments on each section follows afterwards using the same numbering and section headers.

Comments on the statements where consensus was reached (Table 2)

Somatic reporting

The pre-meeting survey showed that in current practice, a majority of responders use a VAF threshold of either 30% or 40% for consideration of whether to include a statement on the report regarding potential germline origin. The delegates felt that a strict cut-off was not helpful, as VAF alone is not a reliable germline indicator and other factors may be taken into consideration (e.g., clinical presentation and family history, performance of panel and nature of variant). The survey and meeting discussions also demonstrated the need for liaison between somatic and germline scientists, in both current and what was felt to be best practice. This process revealed some variability in current practice between different laboratories in the UK. There are also acknowledged differences between UK practice and other countries with established genetic testing services, e.g., in the USA where Molecular Pathologists sign off on somatic NGS reports. Since the consensus meeting in April 2022, the ESMO Precision Medicine Working Group updated its recommendations on follow-up of putative germline variants detected on tumour-only sequencing, with more permissive (lower) thresholds for considering this.[49] Their recommendations after analysis of 49 264 paired tumour-normal samples derive from solid cancers and did not include haematological malignancies.

Confirmatory/predictive germline testing process

Confirmatory testing is done to check if a variant is in the germline after the suggestion of this from the somatic data. Predictive testing means offering a person's relatives a genetic test to clarify if they have inherited a germline variant. Response rates to the pre-meeting survey questions on confirmatory and predictive germline testing were significantly lower than for other questions in the survey. This is because a higher proportion of responders had selected 'not relevant to my role'. In the absence of gene-specific variant interpretation guidance, high level consensus was reached on management of Class 3 VUS involving specialist MDTs, including Clinical Genetics. There are reasons why confirmatory testing may not be feasible prior to offering predictive testing to relatives of a suspected germline variant. These include clinical urgency due to contemporaneous evaluation of a relative who is a potential donor, death of the proband prior to confirmation, or the proband declining germline confirmation for themselves but testing being offered to relatives. The latter situation may give rise to conflicts of interest regarding caring for the proband and caring for the family, which need careful consideration and ethical discussions within MDTs.

Sample selection

In the pre-meeting survey, delegates were asked about current practice regarding sample types used for confirmatory germline testing. Fibroblast-derived DNA from a skin biopsy was shown to be the most common sample type used in both routine and time-sensitive situations (the latter usually because an urgent bone marrow donor is being sought). The in-meeting poll allowed delegates to select and rank sample types considered to be suitable in best practice. The discussions revealed that practice does and will continue appropriately to depend on the exact clinical situation.

Patient information

The pre-meeting survey showed variable practice regarding whether patients are informed of the possibility of finding a (likely) germline variant. There was discussion in the meeting about the advantages/disadvantages of counselling patients regarding the potential to reveal a hereditary predisposition at the point of consenting for somatic testing. The difficulties of doing so in the context of a new diagnosis of leukaemia were discussed, especially when a patient may be in shock and experiencing 'information overload'. The patient representatives contributed to express they felt clear counselling regarding the potential to reveal a hereditary predisposition was important. A comment from the meeting live chat box from a patient representative said: 'Us patients want to know what you might find. Whether or not we want to know what you *did* find is a separate issue, but if you are doing any test on a patient, you must tell them what it might show'. Potential implications for

TABLE 2 Statements on which consensus was reached.

1. Somatic reporting

A statement on the report suggesting possible germline origin of a variant should be considered for any variant where a confirmed germline finding would have potential clinical significance, especially if the variant allele frequency is >30%.
(Agree/Strongly agree: 99%)

*Scientists writing somatic reports should ideally have pre-reporting access (*via *multidisciplinary team (MDT)/email) to germline scientific/clinical expertise when deciding if variants of uncertain significance of potential germline origin (classified as per germline variant interpretation guidelines) should be reported.*
(Agree/Strongly agree: 92%)

Likely pathogenic/pathogenic variants that are clearly clinically actionable in both the somatic and germline context can be reported at time of somatic analysis without further discussion.
(Agree/Strongly agree: 98%)

*Scientists writing somatic reports should ideally have pre-reporting access (*via *MDTs or other routes of communication) to germline scientific/clinical expertise when deciding if variants of uncertain significance of potential germline origin (classified as per germline variant interpretation guidelines) should be reported.*
(Agree/Strongly agree: 92%)

There should be different template phrases for actionability in different contexts, in order to differentiate between variants that are clearly clinically actionable in the germline (likely pathogenic/pathogenic) and those that may be considered a variant of uncertain significance based on germline variant interpretation guidelines.
(Agree/Strongly agree: 99%)

If a variant of potential germline origin is identified during somatic testing, it would be best practice to perform variant classification according to ACMG[2]/CanVIG-UK[20]/ClinGen[4] guidelines in advance of offering the patient site-specific confirmatory germline testing.
(Agree/Strongly agree: 96%)

2. Confirmatory/predictive germline testing process

*It would be best practice to undertake diagnostic germline confirmatory testing in the proband prior to offering cascade germline testing to relatives, although this may not be feasible in all situations (*e.g., *clinical urgency, unexpected death).*
(Agree/Strongly agree: 99%)

If a variant of potential germline origin not directly causative for the phenotype under investigation, but relevant for other disease risks, is incidentally identified during somatic testing, it would be best practice to discuss the case with Clinical Genetics prior to referring patients for confirmatory germline testing.
(Agree/Strongly agree: 85%)

It would be best practice that, if a variant of potential germline origin is identified during somatic testing that is classified as Class 3 (variant of uncertain significance) based on germline variant interpretation guidelines, although confirmatory germline is not usually indicated, it may be justified in certain circumstances after discussion and documentation of purpose and utility of such testing at specialist MDT, including input from Clinical Genetics.
(Agree/Strongly agree: 97%).

If a germline variant of uncertain significance in a gene associated with haematological malignancy is identified in an affected individual, it would be best practice to offer site specific testing to blood relatives only after discussion and documentation regarding rationale for same at specialist MDT, including input from Clinical Genetics.
(Agree/Strongly agree: 96%)

3. Sample selection

The following statement and ranked list of sample options achieved consensus agreement.
Best practice is to arrange confirmatory germline testing using best available sample type as dictated in the hierarchy listed here below. It is reasonable to move down the list if the first option is deemed clinically inappropriate, impractical or impossible.
(Agree/Strongly agree: 87%)

(i) Skin biopsy with cultured fibroblasts.
(ii) Skin biopsy with direct prep/extraction.
(iii) Remission sample.
(iv) Hair root/nail clipping.
(v) Predictive genetic testing in an at-risk relative where testing of proband not possible and variant is at least class 4 and VAF at least 40%.

4. Patient information

It is appropriate to inform patients of the possibility of finding a germline genetic variant when arranging genetic profiling of bone marrow or blood in patients with a known haematological disorder.
(Yes: 96%)

I would support the development of standardised patient information around the possibility of identifying a germline predisposition from somatic testing.
(Agree/Strongly agree: 97%)

It is appropriate for patients with a known haematological disorder to be made aware of the possibility and how to access further information regarding potential of finding germline genetic variant when arranging genetic profiling of bone marrow or blood.
(Yes: 99%)

5. Indications and pathways for referral to Clinical Genetics

It is preferable for confirmatory testing of a likely pathogenic/pathogenic variant of potential germline origin to be arranged by the Haematology team when the patient requires a bone marrow transplant (time sensitive).
(Agree/Strongly agree: 83%)

TABLE 2 (Continued)

There may be scenarios where a repeat somatic NGS panel on a remission blood or bone marrow sample is an appropriate next step to indicate whether germline testing is required. (Agree/Strongly agree: 95%)
There should be a pathway for Clinical Genetics referral prior to diagnostic confirmatory germline testing in complex situations or where early Clinical Genetics input may be helpful. (Agree/Strongly agree: 88%)
It is preferable that healthy relatives are ideally offered genetic counselling via a Clinical Genetics referral prior to consenting and predictive testing for a likely pathogenic/pathogenic familial variant if not being considered as a potential bone marrow donor. (Agree/Strongly agree: 95%)
It is preferable that healthy relatives being considered as a potential bone marrow donor are ideally offered genetic counselling via Clinical Genetics prior to consenting and predictive testing for a likely pathogenic/pathogenic familial variant (with rapid timescale flagged). (Agree/Strongly agree: 96%)
Counselling for predictive testing of children for likely pathogenic/pathogenic familial variants in CEBPA, ANKRD26, ETV6, GATA2, and RUNX1 should be undertaken by the Clinical Genetics team. (Agree/Strongly agree: 93%)
All patients identified as carriers of a likely pathogenic/pathogenic germline variant should be referred to Clinical Genetics for further counselling and cascade screening (if not seen in genetics previously). (Agree/Strongly Agree: 96%)
6. Age at which predictive testing should be offered
The age at which predictive testing is offered to unaffected children at risk of inheriting likely pathogenic/pathogenic variants in CEBPA, ANKRD26, ETV6, GATA2, and RUNX1 should be individualised taking into account the genotype and family history, in liaison with the family. (Agree/Strongly agree: 81%)
Predictive testing of likely pathogenic/pathogenic variants in DDX41 would not typically be offered before adulthood (in line with The British Society for Genetic Medicine (BSGM) guidance on testing in childhood for adult-onset disorders). (Agree/Strongly agree: 96%)
7. Management of carriers
All patients identified as carriers of a likely pathogenic/pathogenic (LP/P) germline variant who develop a blood phenotype (pre-malignant/malignant) should be referred to Haematology for monitoring and follow-up (if not already under care of Haematology). (Agree/Strongly agree: 88%)
Carriers of LP/P variants in CEBPA, ANKRD26, ETV6, GATA2, DDX41 and RUNX1 should be provided with advice about symptom awareness. (Agree/Strongly agree: 94%)
Screening should not be offered until the at-risk individual has been confirmed to have inherited the familial variant (but it is reasonable to arrange baseline full blood count at time of bleeding for genetic testing). (Agree/Strongly agree: 86%)
8. Resources
In order to provide these consensus best practice guidelines, our service would require additional resources. (Agree/Strongly agree: 98%)

family members is already a feature of standardised 'Record of discussion' (consent) forms within NHSE and in consent forms used across the UK. There was consensus that standardised patient information sheets may be helpful in addressing some of these challenges. In line with wider healthcare practice, there should be an option for patients and at-risk relatives who decline testing for germline variants at the time they are offered this to have sufficient time to consider or defer testing until a later time. The meeting did not address the situation where a germline predisposition may be present, but not be detected by the test methodology (e.g., copy number variants and large exon-spanning deletions that are undetected by somatic NGS panel tests).

Indications and pathways for referral to Clinical Genetics

The pre-meeting survey showed that confirmatory germline testing is currently offered at many centres if a suspected germline variant is found on somatic testing for *DDX41, CEBPA, RUNX1, ANKRD26, ETV6* and *GATA2*. Polling questions regarding each gene showed that a greater proportion of delegates considered confirmatory testing would occur in 'ideal' or best practice, compared to the proportion undertaking it in current practice. A similar pattern emerged from questions regarding the subsequent offer of predictive/cascade testing to relatives. There was agreement that Haematology services may be best placed to arrange confirmatory germline testing, with access to Clinical Genetics services as required. There was strong consensus that a referral to Clinical Genetics for genetic counselling is appropriate for relatives as part of offering predictive testing, regardless of age or whether the relative is a potential bone marrow transplant donor.

Age at which predictive testing should be offered

For genes with highly variable penetrance across childhood and adulthood, as well as variable expressivity including non-haematological/myeloid features, the assessment of the situation on a case-by-case basis was considered the best

TABLE 3 Summary of further work underway/planned.

Identified area for further work	National Body Progressing Work
Standardisation of somatic reporting templates	Somatic Variant Interpretation Group (S-VIG) a subgroup of the ACGS[4]
Germline gene specific variant interpretation guidelines	Cancer Variant Interpretation Group UK (CanVIG-UK)[20]
Carrier database and longitudinal phenotype/genotype data capture	UKCGG,[19] NHS England via Genomic Medicine Service Alliances[50] and Genomic Laboratory Hubs,[51] NHS Digital[52]
Gene specific carrier guidelines	UKCGG,[19] CanGene-CanVar research programme,[20] NHS England[53]
National standardised patient information	UKCGG,[19] patient groups and charities
National development of educational materials for the NHS workforce	Genomics Education Programme of Health Education England,[54] UKCGG,[19] CanGene-CanVar research programme,[20] Association of Genetic Nurses and Counsellors (AGNC)[55]
Bone marrow transplant/donor focused consensus workshop: held 15th July 2022. Findings to be published in an aligned article in 2023	British Society of Blood and Marrow Transplantation and Cellular Therapy[56]/UKCGG[19]

practice by delegates. Regarding *DDX41*, with a usually later adult-onset phenotype overlapping with the average age of sporadic acute myeloid leukaemia in the general population, delegates felt it would rarely be appropriate to consider predictive testing before adulthood.

Management of carriers

The pre-meeting survey showed that a minority of centres are currently offering any kind of screening (e.g., full blood counts, clinical examination, blood films) to heterozygous carriers of *CEBPA, ANKRD26, ETV6, GATA2, DDX41* and *RUNX1* who currently have no blood phenotype. In these centres offering any screening, the most common method was an annual full blood count. Consensus was not reached on whether screening should be offered to heterozygous carriers with no blood phenotype or what the type or frequency of screening should involve. It was felt that a referral to Haematology would be appropriate by most delegates once a blood phenotype was detected. *DDX41* was identified as having different considerations to the other genes, given the comparative late age of onset of disease.

Resources

Further work is needed to establish how data related to carriers can be robustly captured on a prospective basis, and we hope the findings from this meeting can be leveraged to support applications for additional resources in this regard.

DISCUSSION

This is the first UK meeting to address clinical and laboratory pathways for patients with (or suspected) germline predisposition to haematological malignancy. The strength of the guidance derives from UK-wide invitation (no number cap for this virtual meeting or disadvantage due to travel). Key issues were selected for the agenda based on seeking opinion prior to the meeting, and there was attendance from broad specialties including patient advocates. The different perspectives and expertise of the group enriched the discussion and allowed the group to achieve consensus views on several aspects.

Consensus was reached on best practice relating to somatic reporting, confirmatory testing of suspected germline variants, suitability of different sample types, the need for patient information/support and MDT working including Clinical Genetics input.

Key recommendations from stakeholders who participated in this meeting can be summarised as:

1. There should be close liaison between somatic and germline teams for variant interpretation
2. There is a need for MDT working to provide the best patient care
3. Prospective data should be collected to inform future best practice

Despite consideration, discussion and re-framing of proposed best practice statements, we could not reach consensus regarding the type and frequency of screening, or if screening should be offered at all to carriers of likely pathogenic/pathogenic variants in *DDX41, CEBPA, ANKRD26, ETV6, GATA2*, and *RUNX1*. Over the course of the discussion, it became increasingly evident that gene-specific guidance is required and that there is a lack of evidence regarding the utility of screening in this patient group.

Unique challenges arose related to donor selection for those patients requiring allogenic transplant when potential related donors carry/are at risk of inheriting a constitutional variant predisposing to haematological malignancy.

Further work is needed to develop gene-specific variant interpretation guidance, to capture prospective data with associated funding and infrastructure, and to further develop/share patient and educational materials. Discussions related to this theme were deferred to a separate dedicated workshop in collaboration with British Society of Blood and Marrow Transplantation and other key stakeholders. This consensus meeting provided the national impetus and collaboration to progress this work in a number of areas (Table 3).

AUTHOR CONTRIBUTIONS

All named authors were part of the organising committee and contributed significantly to the planning, delivery or manuscript preparation. All named authors have reviewed the manuscript and approved this for submission. Katie Snape and Terri P. McVeigh – conceptualisation, organisation of meeting, oversight of process and review of manuscript. Beverley Speight – organisation/delivery of meeting, writing first draft and editing with co-author comments. Angela Hamblin and Polly Talley organisation/delivery of meeting and review of article. Helen Hanson, Clare Turnbull, Steven Hardy, James Drummond, Jamshid Khorashad, Christopher Wragg, Paula Page, Nicholas W. Parkin, Ana Rio-Machin, Jude Fitzgibbon, Austin Gladston Kulasekararaj contribution to meeting and review of the article.

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CONFLICT OF INTEREST STATEMENT

No conflicting/competing interests declared.

ETHICS APPROVAL

Not required.

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