Appendix 3. Pre-meeting survey questions

Demographic information

1. **What is your role?**

Consultant Clinical Geneticist

Genetic Counsellor

Clinical Scientist (somatic)

Clinical Scientist (germline)

Clinical Scientist (somatic and germline)

Consultant Adult Haematologist

Consultant Paediatric Haematologist

Clinical Nurse Specialist

Researcher (scientist)

Researcher (clinical academic)

Patient representative

Other

1. **If applicable, in which Genomic Laboratory Hub/region do you work?**

Central and South Genomic Laboratory Hub led by Birmingham Women’s and Children NHS Foundation Trust

East Genomic Laboratory Hub led by Cambridge University Hospitals NHS Foundation Trust

North West Genomic Laboratory Hub led by Manchester University NHS Foundation Trust

North Thames Genomic Laboratory Hub led by Great Ormond Street Hospital for Children NHS Foundation Trust

South East Genomic Laboratory Hub led by Guy’s and St Thomas’ NHS Foundation Trust

South West Genomic Laboratory Hub led by North Bristol NHS Trust

North East and Yorkshire Genomic Laboratory Hub led by The Newcastle upon Tyne Hospitals NHS Foundation Trust

Scotland

Wales

Northern Ireland

Other

Not applicable

Assessment and reporting of variants of potential germline origin

**Please review the process flow here below.**

 **We will now ask you to respond to queries regarding processes in your institution.**GTAB = Genomic Tumour Advisory Board

The next questions refer to somatic only testing i.e. where genomic testing is performed on diseased blood/bone marrow (tumour DNA) WITHOUT a paired germline (constitutional DNA) sample.

1. **At present,**in your centre which of the following genes that confer germline predisposition to haematological phenotypes are included on your somatic (tumour-only) panel. Select all that apply

DDX41

CEBPA

RUNX1

ANKRD26

ETV6

GATA2

BRCA1

BRCA2

PALB2

ATM

CHEK2

All of the above

Not applicable to my job role

Others

1. If you ticked "other" please list the genes you include on your somatic (tumour-only) panel which may also confer germline predisposition to haematological conditions.
2. At what Variant Allele Frequency (VAF) threshold would you include a statement that the variant may be of germline origin for variants identified in pre-treated (at diagnosis) diseased blood/bone marrow on somatic (tumour-only testing)?

30% or higher

40% or higher

50% or higher

Don't know

other

not applicable

Clinical infrastructure and pathways

1. **At present,**in your centre, who attends your multidisciplinary team meeting/genomic tumour advisory board? Select all that apply.

GTAB/MDT co-ordinator

Haematologist

Clinical nurse specialist

Somatic scientist

Germline scientist

Clinical Geneticist

Genetic counsellor

Bioinformatician

Pathologist

No official GTAB/MDT in place at present

Other

1. If other, please specify who else attends your GTAB/MDT?
2. **For clinicians:** **At present,**in your centre, when undertaking genetic profiling on bone marrow/blood of patients with an active haematological malignancy, do you counsel patients regarding the possibility of inadvertently identifying a constitutional (germline) genetic variant?

Yes

Sometimes

No

I don’t know

Not relevant to my role

1. **For clinicians:** when consenting patients for genomic profiling of their blood/bone marrow, what type of consent is obtained?

Written

Verbal

Consent not explicitly obtained for testing beyond bone marrow collection procedure

I don't know

Not relevant to my role

Clinical pathways and confirmatory testing

1. Please state your level of agreement with the following statements:

**Ideally,** germline confirmatory testing of variants identified on somatic (tumour-only) testing should take place in the following scenarios:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Strongly disagree | Disagree | Neutral  | Agree | Strongly agree | I don’t know  |
| Variants in genes for which germline genetic testing is available as per germline test directory |  |  |  |  |  |  |
| Variants in genes associated with the clinical phenotype (“on tumour”) |  |  |  |  |  |  |
| Variants in genes not necessarily causative for the patient phenotype but associated with high risk of another phenotype (e.g.*BRCA1*) |  |  |  |  |  |  |
| Variants in genes not necessarily causative for the patient phenotype but associated with moderate risk of another phenotype (e.g.*CHEK2*) |  |  |  |  |  |  |
| Heterozygous Variants in genes associated with recessive disorders where population carrier frequency is 1 in 70 or higher |  |  |  |  |  |  |
| Heterozygous Variants in genes associated with rare recessive disorders where population carrier frequency is rarer than 1 in 70 |  |  |  |  |  |  |
| Variant identified in sample from an adult in a gene associated with a syndromic disorder where phenotype usually evident in childhood and phenotype is unknown in patient |  |  |  |  |  |  |

1. **At present,**in your centre when confirmatory germline genetic testing is required, which sample type is used preferentially in the following scenarios

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Blood with cell sorting to avoid | Fibroblast-derived DNA (skin) | Buccal swab | Hair root/nail | I don't know | Not relevant to my role | It varies |
| If urgent bone marrow transplant is not required (not time sensitive) |  |  |  |  |  |  |  |
| If urgent bone marrow transplant is not required (not time sensitive) |  |  |  |  |  |  |  |

1. Are any other samples used for confirmation of germline origin of variants not mentioned here above?
2. **At present** in your centre,counselling and consenting of patients for germline genetic testing is undertaken by whom in the following scenarios

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Geneticist/Genetic Counsellor | Haematologist/haematology CNS | Clinical geneticist/Genetic Counsellor or haematologist | other | I don't know | not applicable | It varies |
| Confirmatory testing of variant identified in tumour in an affected patient to confirm germline origin when the patient requires bone marrow transplant (time sensitive) |  |  |  |  |  |  |  |
| Confirmatory testing of variant identified in tumour in an affected patient to confirm germline origin when the patient does not require bone marrow transplant (NOT time sensitive) |  |  |  |  |  |  |  |
| Predictive testing in unaffected relatives being considered as bone marrow donors for their affected relatives (time sensitive) |  |  |  |  |  |  |  |
| Predictive testing in unaffected relatives when bone marrow donation is not required (NOT time sensitive) |  |  |  |  |  |  |  |

1. If other, **at present**in your centre who undertakes counselling and consenting of patients for germline genetic testing (please specify urgency)
2. **In an ideal** clinical pathway, what would be your preferred option for counselling and consenting of patients for germline genetic testing in the following scenarios

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Geneticist/Genetic Counsellor | Haematologist/haematology CNS | Clinical geneticist/Genetic Counsellor or haematologist | other | I don't know | not applicable | It varies |
| In an affected patient to confirm a somatic (tumour-only) variant of potential germline when the patient requires bone marrow transplant (time sensitive) |  |  |  |  |  |  |  |
| In an affected patient to confirm a somatic (tumour-only) variant of potential germline when the patient does not require bone marrow transplant (NOT time sensitive) |  |  |  |  |  |  |  |
| Predictive testing in unaffected relatives being considered as bone marrow donors for their affected relatives (time sensitive) |  |  |  |  |  |  |  |
| Predictive testing in unaffected relatives when bone marrow donation is not required (NOT time sensitive) |  |  |  |  |  |  |  |

1. If other, **ideally**in your centre who would undertake counselling and consenting of patients for germline genetic testing (please specify urgency)
2. **At present**in your centre, when a variant of germline origin is identified in a patient with a haematological malignancy requiring bone marrow transplant, which of the following classes of variant would you offer testing to relatives for (select all that apply)

Class 5 Pathogenic variants/Class 4 Likely pathogenic variants

Class 3 Suspicious "hot" VUS

Class 3 Unsuspicious "cool/cold" VUS

All of the above

I don't know

1. **At present**in your centre, where a potential related donor is found to carry the genetic variant identified in their affected family member, when, if ever, would you still consider them as a potential donor

Never

If no available related donor available

Would not consider this a contraindication to donation

Would depend on the gene/clinical situation

I don't know

Other

Management pathways for *CEBP1, ANKRD26, ETV6, GATA2, DDX41, RUNX1*

1. **At present**in your centre, please specify if you offer the following management when Class 4/5 likely pathogenic/pathogenic variants of suspected germline origin are identified in the genes listed here below: **Confirmatory germline diagnostic testing is offered where a variant of potential germline origin is identified on somatic (tumour-only) testing**

*CEPBA*

*ANKRD26*

*ETV6*

*GATA2*

*DDX41*

*RUNX1*

1. **In an ideal clinical pathway**in your centre, please specify if you want to offer the following management when Class 4/5 likely pathogenic/pathogenic variants of suspected germline origin are identified in the genes listed here below: **Confirmatory germline diagnostic testing is offered where a variant of potential germline origin is identified on somatic (tumour-only) testing**

*CEPBA*

*ANKRD26*

*ETV6*

*GATA2*

*DDX41*

*RUNX1*

1. **At present**in your centre, please specify if you offer the following management when Class 4/5 likely pathogenic/pathogenic variants of suspected germline origin are identified in the genes listed here below: **If a germline variant is confirmed, predictive/cascade testing is offered to  blood relatives**

*CEPBA*

*ANKRD26*

*ETV6*

*GATA2*

*DDX41*

*RUNX1*

1. **In an ideal clinical pathway**in your centre, please specify if you want to offer the following management when Class 4/5 likely pathogenic/pathogenic variants of suspected germline origin are identified in the genes listed here below: **If a germline variant is confirmed, predictive/cascade testing is offered to  blood relatives**

*CEPBA*

*ANKRD26*

*ETV6*

*GATA2*

*DDX41*

*RUNX1*

1. **At present**in your centre, please specify if you offer the following management when Class 4/5 likely pathogenic/pathogenic variants of suspected germline origin are identified in the genes listed here below: **Screening is offered to unaffected carriers**

*CEPBA*

*ANKRD26*

*ETV6*

*GATA2*

*DDX41*

*RUNX1*

1. **In an ideal clinical pathway**in your centre, please specify if you want to offer the following management when Class 4/5 likely pathogenic/pathogenic variants of suspected germline origin are identified in the genes listed here below: **Screening is offered to unaffected carriers**

*CEPBA*

*ANKRD26*

*ETV6*

*GATA2*

*DDX41*

*RUNX1*

Carrier management: *CEBPA*

1. **At present**in your centre, for ***CEPBA***, what screening would you offer for UNAFFECTED gene carriers

No screening

Annual Full Blood Count (FBC)

Full Blood Count (FBC) different frequency (specify in free text box below)

Annual NGS/Myeloid panel

NGS/Myeloid panel different frequency (specify in free text box below)

Annual Bone Marrow +/- cytogenetic/NGS analysis

Bone marrow different frequency (specify in free text box below)

Other

Don't know

1. Please specify if you chose other or different frequency
2. **In an ideal clinical pathway**in your centre, for ***CEPBA***, what screening would you offer for UNAFFECTED gene carriers

No screening

Annual Full Blood Count (FBC)

Full Blood Count (FBC) different frequency (specify in free text box below)

Annual NGS/Myeloid panel

NGS/Myeloid panel different frequency (specify in free text box below)

Annual Bone Marrow +/- cytogenetic/NGS analysis

Bone marrow different frequency (specify in free text box below)

Other

Don't know

1. Please specify if you chose other or different frequency

Carrier management: *ANKRD26*

1. **At present**in your centre, for ***ANKRD26***, what screening would you offer for UNAFFECTED gene carriers

No screening

Annual Full Blood Count (FBC)

Full Blood Count (FBC) different frequency (specify in free text box below)

Annual NGS/Myeloid panel

NGS/Myeloid panel different frequency (specify in free text box below)

Annual Bone Marrow +/- cytogenetic/NGS analysis

Bone marrow different frequency (specify in free text box below)

Other

Don't know

1. Please specify if you chose other or different frequency
2. **In an ideal clinical pathway**in your centre, for ***ANKRD26***, what screening would you offer for UNAFFECTED gene carriers

No screening

Annual Full Blood Count (FBC)

Full Blood Count (FBC) different frequency (specify in free text box below)

Annual NGS/Myeloid panel

NGS/Myeloid panel different frequency (specify in free text box below)

Annual Bone Marrow +/- cytogenetic/NGS analysis

Bone marrow different frequency (specify in free text box below)

Other

Don't know

1. Please specify if you chose other or different frequency

Carrier management: *ETV6*

1. **At present**in your centre, for ***ETV6***, what screening would you offer for UNAFFECTED gene carriers

No screening

Annual Full Blood Count (FBC)

Full Blood Count (FBC) different frequency (specify in free text box below)

Annual NGS/Myeloid panel

NGS/Myeloid panel different frequency (specify in free text box below)

Annual Bone Marrow +/- cytogenetic/NGS analysis

Bone marrow different frequency (specify in free text box below)

Other

Don't know

1. Please specify if you chose other or different frequency
2. **In an ideal clinical pathway**in your centre, for ***ETV6***, what screening would you offer for UNAFFECTED gene carriers

No screening

Annual Full Blood Count (FBC)

Full Blood Count (FBC) different frequency (specify in free text box below)

Annual NGS/Myeloid panel

NGS/Myeloid panel different frequency (specify in free text box below)

Annual Bone Marrow +/- cytogenetic/NGS analysis

Bone marrow different frequency (specify in free text box below)

Other

Don't know

1. Please specify if you chose other or different frequency

Carrier management: *GATA2*

1. **At present**in your centre, for ***GATA2***, what screening would you offer for UNAFFECTED gene carriers

No screening

Annual Full Blood Count (FBC)

Full Blood Count (FBC) different frequency (specify in free text box below)

Annual NGS/Myeloid panel

NGS/Myeloid panel different frequency (specify in free text box below)

Annual Bone Marrow +/- cytogenetic/NGS analysis

Bone marrow different frequency (specify in free text box below)

Other

Don't know

1. Please specify if you chose other or different frequency
2. **In an ideal clinical pathway**in your centre, ***GATA2***, what screening would you offer for UNAFFECTED gene carriers

No screening

Annual Full Blood Count (FBC)

Full Blood Count (FBC) different frequency (specify in free text box below)

Annual NGS/Myeloid panel

NGS/Myeloid panel different frequency (specify in free text box below)

Annual Bone Marrow +/- cytogenetic/NGS analysis

Bone marrow different frequency (specify in free text box below)

Other

Don't know

1. Please specify if you chose other or different frequency

Carrier management: *DDX41*

1. **At present**in your centre, for ***DDX41***, what screening would you offer for UNAFFECTED gene carriers

No screening

Annual Full Blood Count (FBC)

Full Blood Count (FBC) different frequency (specify in free text box below)

Annual NGS/Myeloid panel

NGS/Myeloid panel different frequency (specify in free text box below)

Annual Bone Marrow +/- cytogenetic/NGS analysis

Bone marrow different frequency (specify in free text box below)

Other

Don't know

1. Please specify if you chose other or different frequency
2. **In an ideal clinical pathway**in your centre, ***DDX41***, what screening would you offer for UNAFFECTED gene carriers

No screening

Annual Full Blood Count (FBC)

Full Blood Count (FBC) different frequency (specify in free text box below)

Annual NGS/Myeloid panel

NGS/Myeloid panel different frequency (specify in free text box below)

Annual Bone Marrow +/- cytogenetic/NGS analysis

Bone marrow different frequency (specify in free text box below)

Other

Don't know

1. Please specify if you chose other or different frequency

Carrier management: *RUNX1*

1. **At present**in your centre, for ***RUNX1***, what screening would you offer for UNAFFECTED gene carriers

No screening

Annual Full Blood Count (FBC)

Full Blood Count (FBC) different frequency (specify in free text box below)

Annual NGS/Myeloid panel

NGS/Myeloid panel different frequency (specify in free text box below)

Annual Bone Marrow +/- cytogenetic/NGS analysis

Bone marrow different frequency (specify in free text box below)

Other

Don't know

1. Please specify if you chose other or different frequency
2. **In an ideal clinical pathway**in your centre, ***RUNX1***, what screening would you offer for UNAFFECTED gene carriers

No screening

Annual Full Blood Count (FBC)

Full Blood Count (FBC) different frequency (specify in free text box below)

Annual NGS/Myeloid panel

NGS/Myeloid panel different frequency (specify in free text box below)

Annual Bone Marrow +/- cytogenetic/NGS analysis

Bone marrow different frequency (specify in free text box below)

Other

Don't know

1. Please specify if you chose other or different frequency

Cascade screening and management of carriers

1. Considering variants in the following genes associated with haematological malignancy, from what age do you offer **predictive genetic testing** (if at all) in unaffected relatives

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Childhood | >18 | later adulthood | I don't know | predictive testing not offered  |
| DDX41 |  |  |  |  |  |
| CEBPA |  |  |  |  |  |
| ETV6 |  |  |  |  |  |
| ANRKD26 |  |  |  |  |  |
| GATA2 |  |  |  |  |  |
| RUNX1 |  |  |  |  |  |

1. Considering variants in the following genes associated with haematological malignancy, from what age do you offer **screening** (if at all) in unaffected relatives

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Childhood | >18 | >40 | >50 | I don't know | predictive testing not offered  |
| DDX41 |  |  |  |  |  |  |
| CEBPA |  |  |  |  |  |  |
| ETV6 |  |  |  |  |  |  |
| ANRKD26 |  |  |  |  |  |  |
| GATA2 |  |  |  |  |  |  |
| RUNX1 |  |  |  |  |  |  |

Final questions!

1. Finally, how strongly do you agree with the following statements:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Strongly disagree | Disagree | Neutral  | Agree | Strongly agree | I don’t know  | Not applicable  |
| Clear standardised national guidelines for somatic (tumour-only) tests on reporting of variants of possible germline origin is required |  |  |  |  |  |  |  |
| Our centre would adopt a standardised approach to variant reporting for somatically identified variants of possible germline origin |  |  |  |  |  |  |  |
| A national registry of genotype/phenotype data for genes predisposing to myeloid neoplasias would enable evidence based screening guidelines to be developed and improve patient care |  |  |  |  |  |  |  |
| Our centre would happy to contribute to a national registry of genotype/phenotype information assuming all regulatory approvals/ethics met |  |  |  |  |  |  |  |
| Our centre would support a collaborative national effort between clinicians and scientists to improve the classification of germline Variants of Uncertain Significance (VUS) in genes predisposing to myeloid neoplasms |  |  |  |  |  |  |  |
| National standardised guidelines on the clinical management of gene carriers are required to ensure consistent clinical practice |  |  |  |  |  |  |  |

1. Any other comments?