Germline Predisposition to Haematological Malignancies National Consensus Meeting April 28th and 29th 2022

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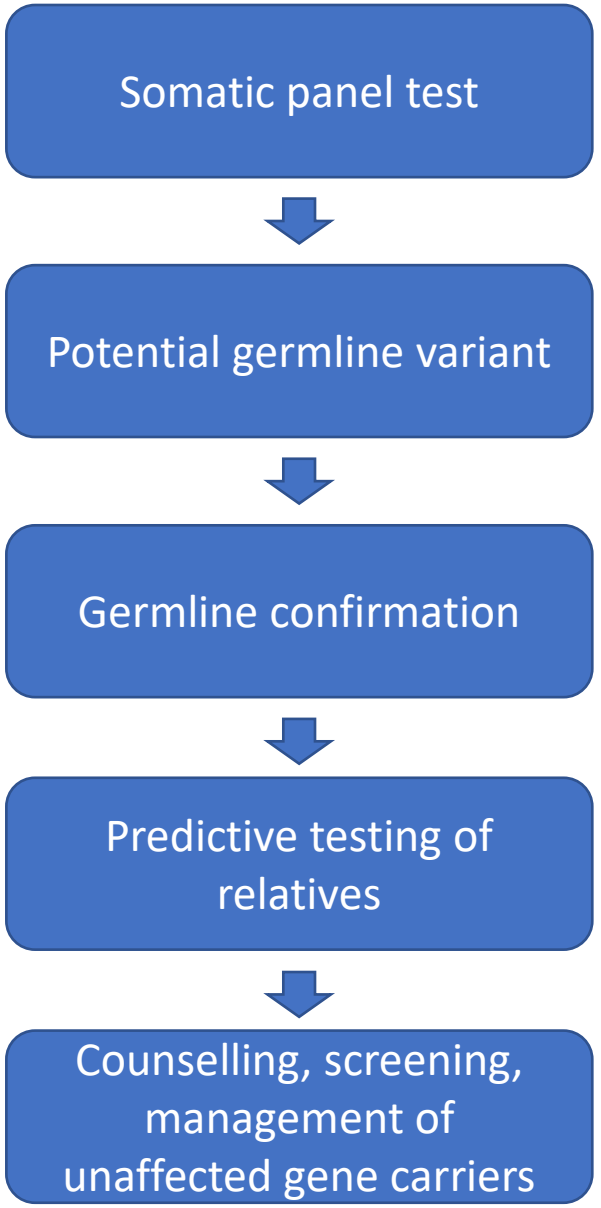
Funded by CANCER RESEARCH UK

Introduction

- Somatic genetic testing in MDS/AML is identifying an increasing number of patients with variants in genes which *might* also indicate germline predisposition to haematological phenotype/malignancies
- The pathways for reporting these somatic variants, undertaking diagnostic germline testing and offering predictive testing to relatives vary across the UK without current clear national guidance
- There is inconsistent practice across the UK with respect to screening and management of unaffected gene carriers



Remit of meeting

- **Huge topic: cannot possibly solve all challenges in 2 half days**

- Meeting aims:

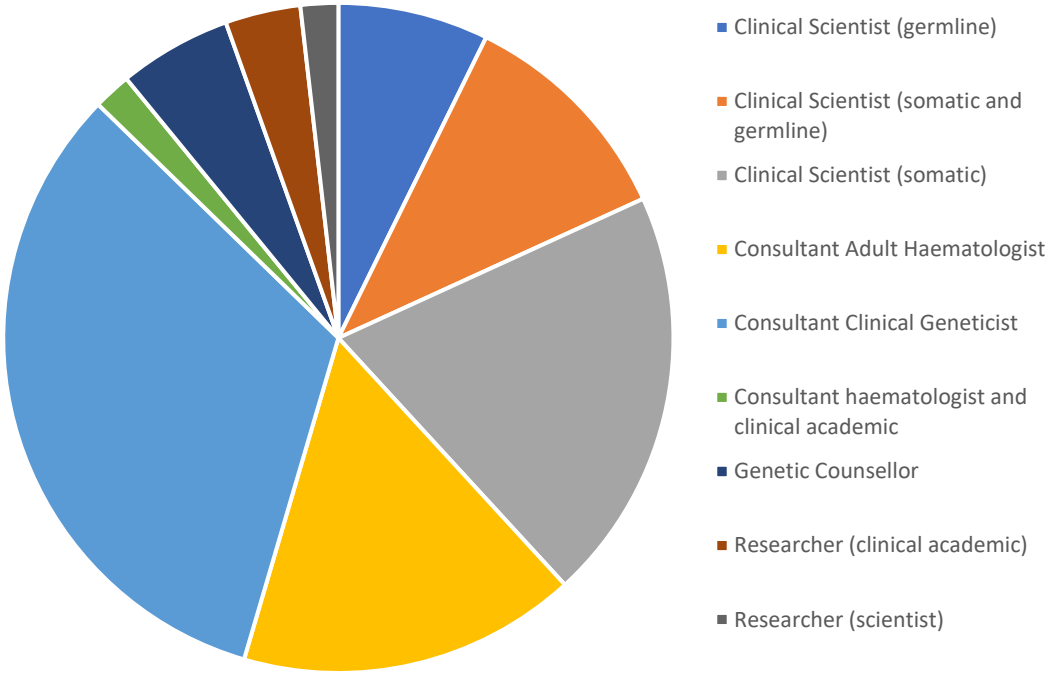
  - To obtain a snapshot of current practice across the UK, highlight issues through case exemplars and confirm the requirement for a more unified approach to shared issues

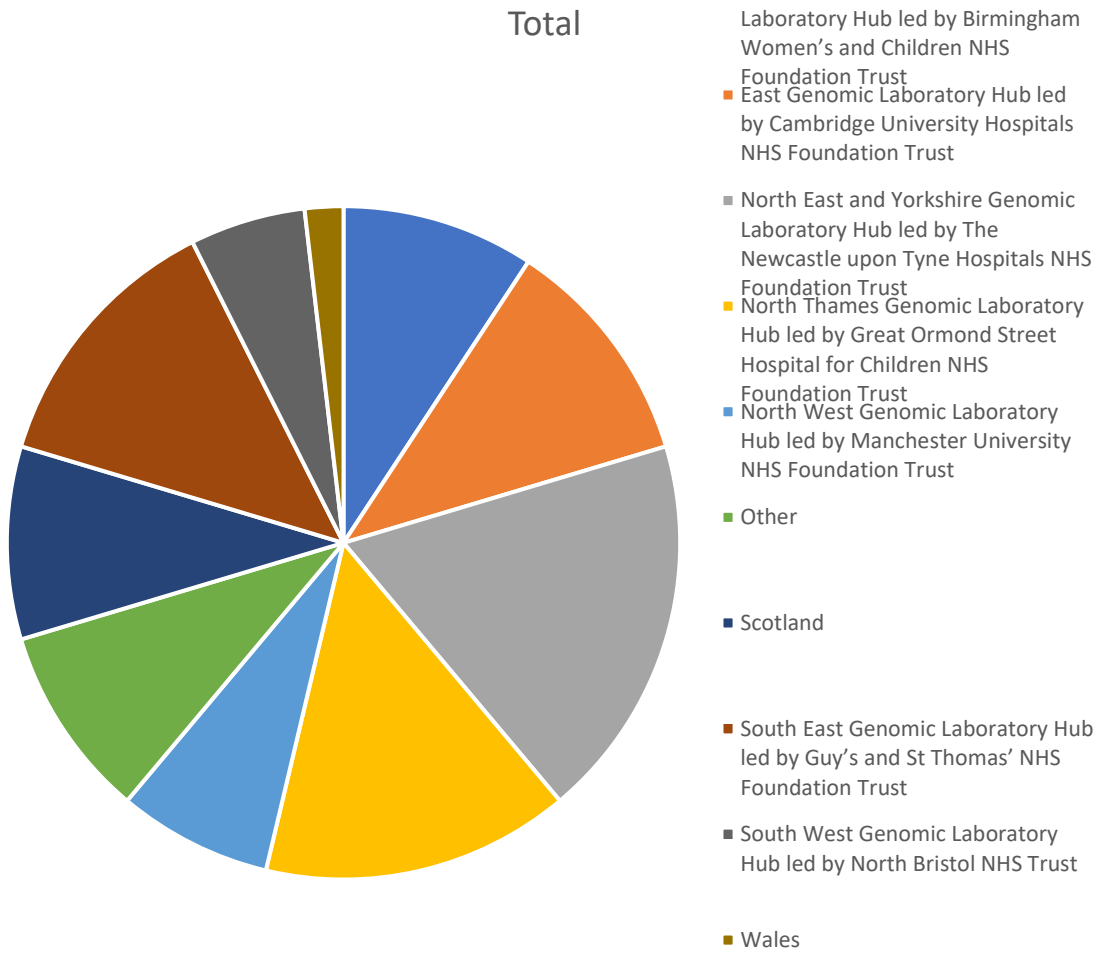
  - To bring UK clinicians, scientists, policy makers and patient reps in one place together to begin the conversation of how we develop a national infrastructure to address these issues

Remit of meeting

- To provide stakeholder consensus on the requirement for standardised national guidance for leverage to national bodies to **progress this work**
  - For example:
    - The minimum requirement/wording for somatic test reports
    - Guidance on what/how/when we should undertake germline confirmation of somatically identified variants
    - Gene-specific standardised guidelines for germline variant interpretation in genes predisposing to haematological malignancies
    - The requirement for an infrastructure to collect genotype : phenotype data through a national register
    - Clear gene-specific guidelines on clinical management and mechanism for iterative review of guidelines

Survey results: Demographics





Key points: **Mix of Clinicians (genetics/haem) and Scientists/Researchers plus patient rep**
Good geographical representation

Patient voice

- Patient/charity representation

CanGene CanVar

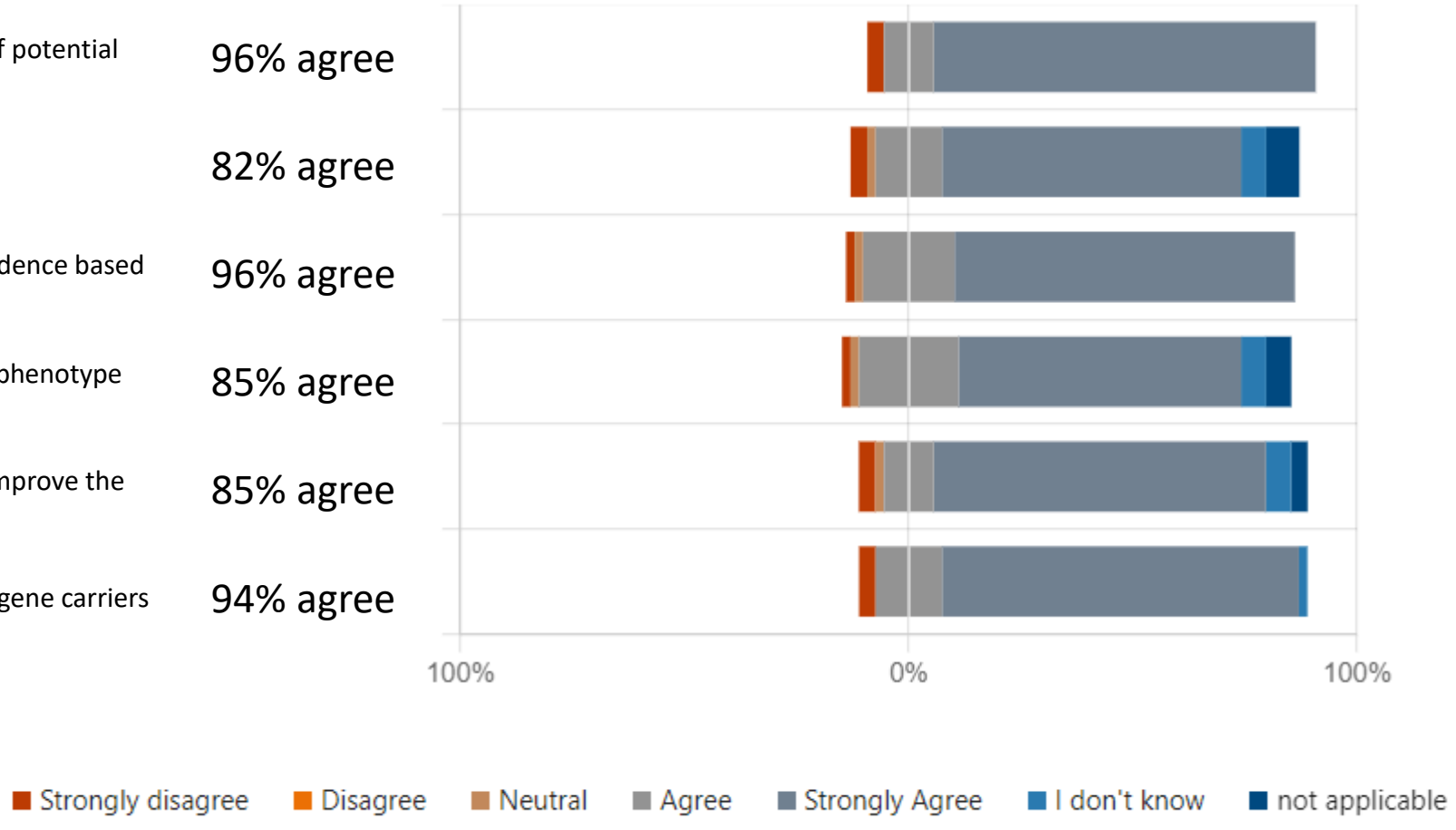
Funded by CANCER RESEARCH UK

Leukaemia Care

YOUR Blood Cancer Charity

Survey results: strong consensus on need

Clear guidelines for reporting of somatically-identified variants of potential germline origin is required	96% agree
Our centre would adopt a standardised approach to reporting	82% agree
National registry for genotype/phenotype data would enable evidence based guidelines to be developed and improve patient care	96% agree
Our centre would contribute to a national registry for genotype/phenotype data	85% agree
Our centre would support a collaborative national approach to improve the classification of germline variants of uncertain significance	85% agree
National standardised guidelines for management of unaffected gene carriers are required to ensure consistent clinical practice	94% agree

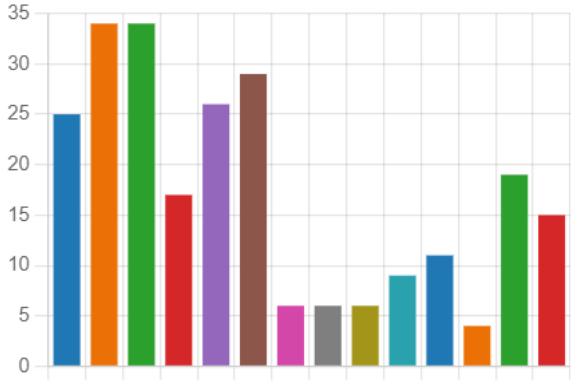


Somatic panels containing CSGs

6. **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 (0 point)

More Details

DDX41	25
CEBPA	34
RUNX1	34
ANKRD26	17
ETV6	26
GATA2	29
BRCA1	6
BRCA2	6
PALB2	6
ATM	9
CHEK2	11
All of the above	4
Not applicable to my job role	19
Others	15



Most common other genes:
TP53
SH2B3
PTPN11
NF1

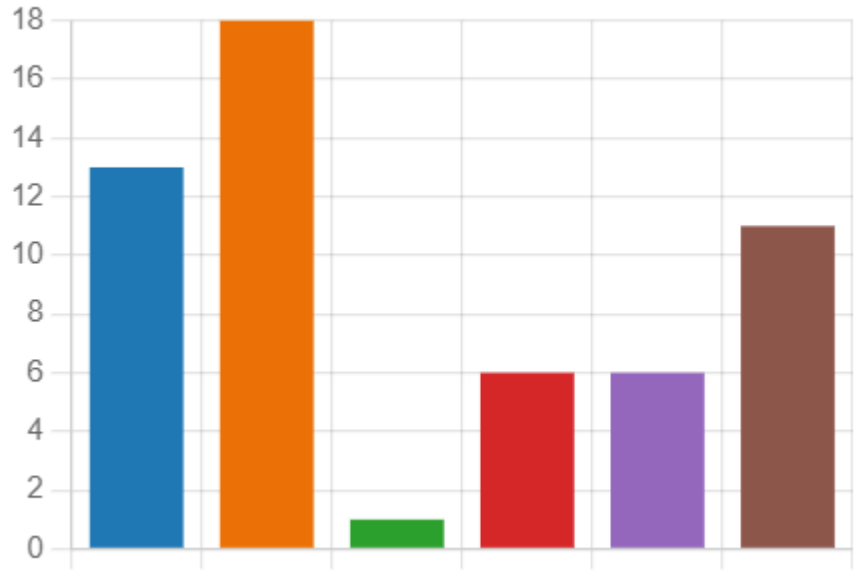
Few centres doing larger panels with more ***cancer susceptibility genes (CSGs)*** *on*

Key points: **All somatic panels contain some genes with potential germline predisposition.**
There is variation in what is being tested somatically.

Variant allele frequencies for stating “possible germline”

More Details

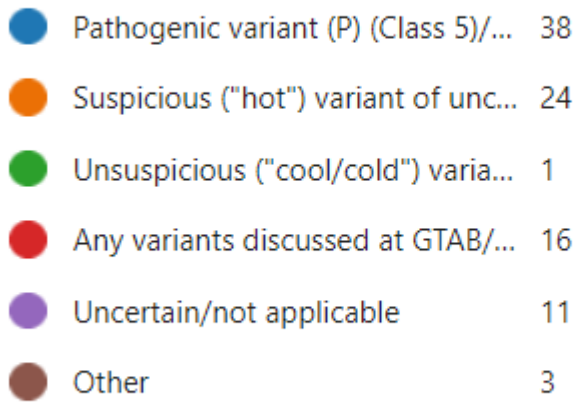
30% or higher	13
40% or higher	18
50% or higher	1
Don't know	6
other	6
not applicable	11

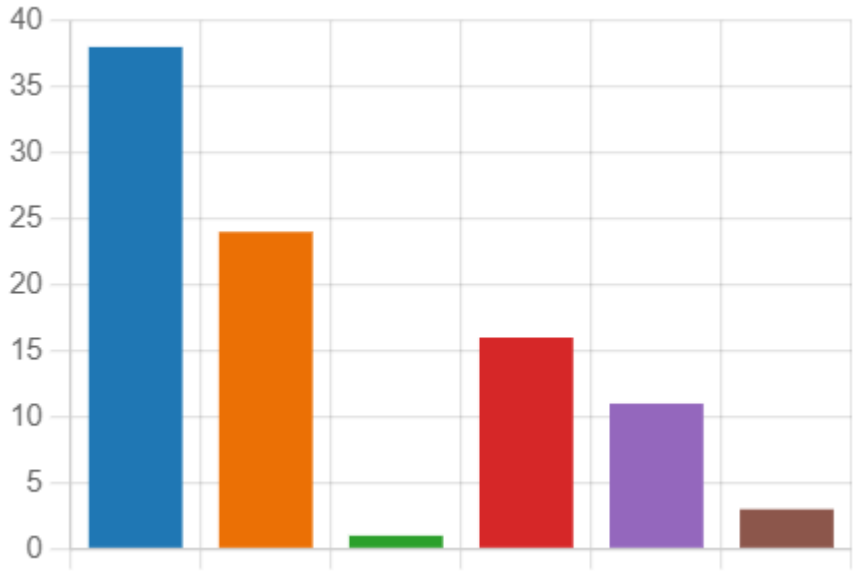


Key points: Varies between labs

Additional info beyond VAF might be taken into consideration when deciding e.g. clinical info/FHx

Types of reported variants on somatic reports



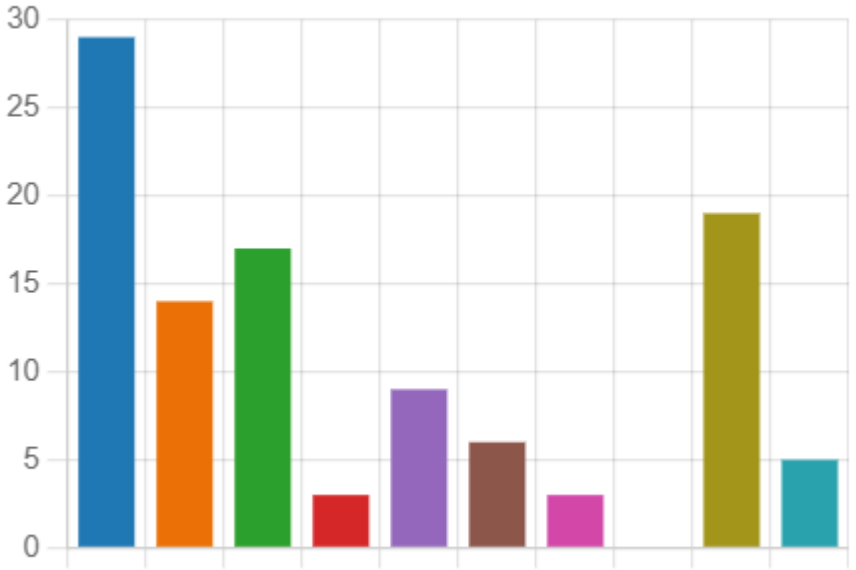


Key points: **Difficult as somatic and germline interpretations not necessarily the same**
Most centres reporting at least some uncertain variants

Types of reported variants on somatic reports

Key point: Practice varies across laboratories

Class 4/5 LP/P in genes **causative** of the patient's phenotype
Class 3 (VUS) in genes **causative** of the patient's phenotype
Class 4/5 LP/P in genes not associated by with other known phenotype (incidental findings)
Class 3 (VUS) in genes not associated by with other known phenotype
Class 4/5 LP/P heterozygous variants for **incidental recessive traits (carrier status)**
Any variant thought to be of germline origin after discussion at MDT
Any variant thought to be of germline origin
We do not include statements regarding germline origin of variants
Uncertain/don't know
Other

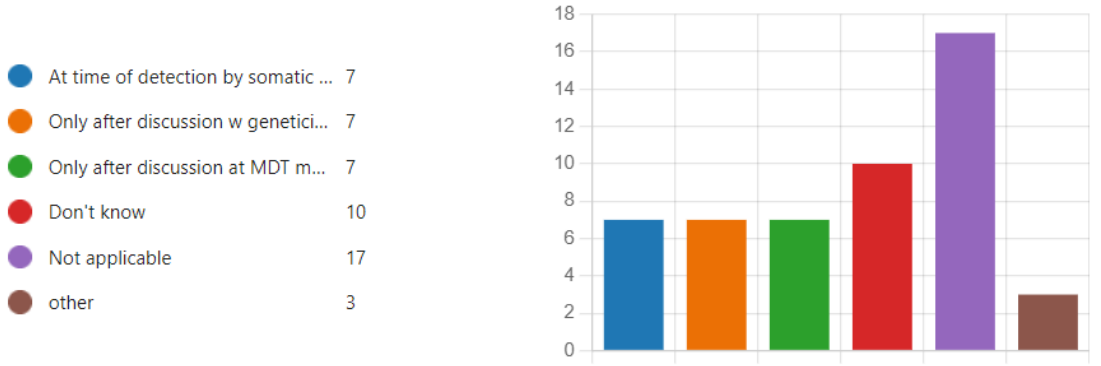


Key points: Varies between labs

Lots of uncertainty by scientists and clinicians of what their local procedures are

When is a decision to report uncertain variants made?

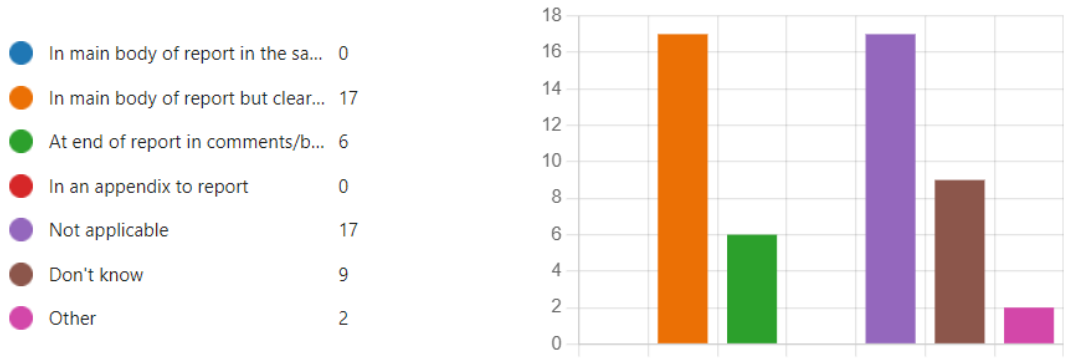
When is a decision made to report?



Where on report are variants reported?

12. **At present,** in your centre, if Class 3 VUS are reported in your centre - where is this information included? (0 point)

More Details



Key points: Varies between labs, potentially due to different infrastructure

Counselling and consenting for somatic testing

- Low numbers
- Variable practice

- Patient view:
- The experience at Genomics England and elsewhere suggests that we 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

20. **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?

More Details

Yes	2
Sometimes	3
No	3
I don't know	6
Not relevant to my role	34

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

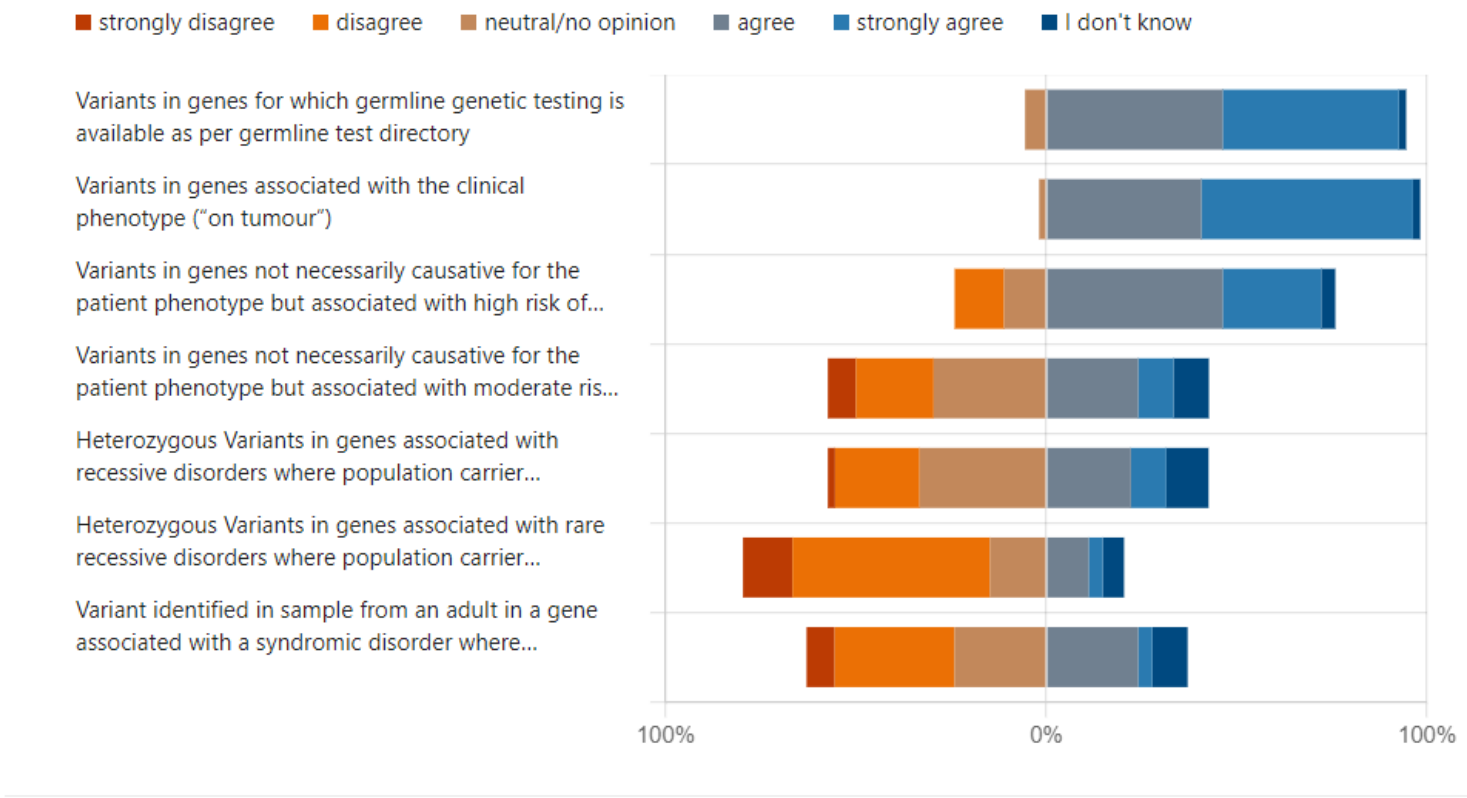
More Details

Written	5
Verbal	3
Consent not explicitly obtained ...	2
I don't know	6
Not relevant to my role	32

What types of variants should be tested?

Key points:

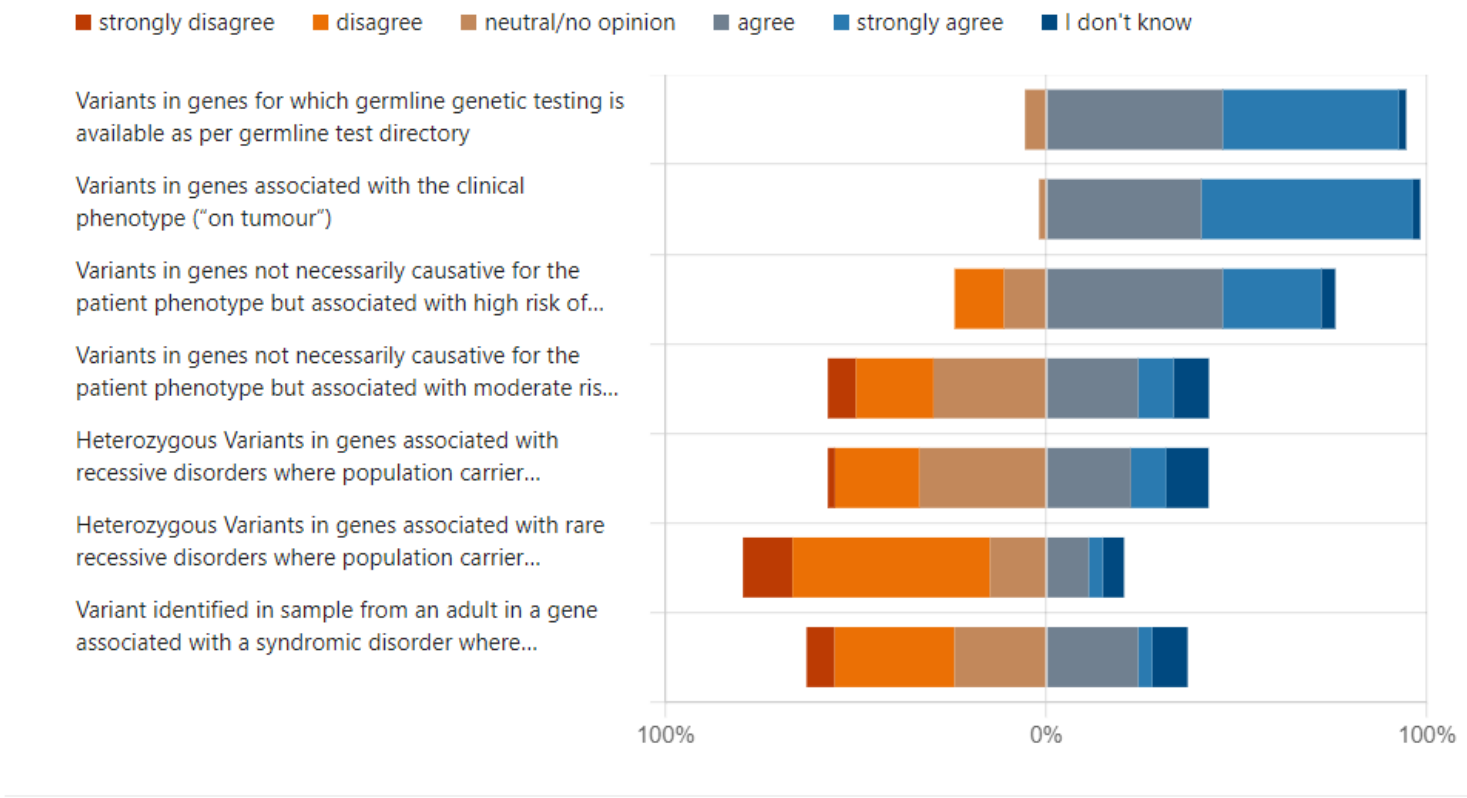
- **>80% Agreement to test genes in germline rare disease test directory**
- **>80% Agreement to test genes associated with phenotype**
- **>70% Agreement to test genes not associated with phenotype but with clinical utility (incidental)**



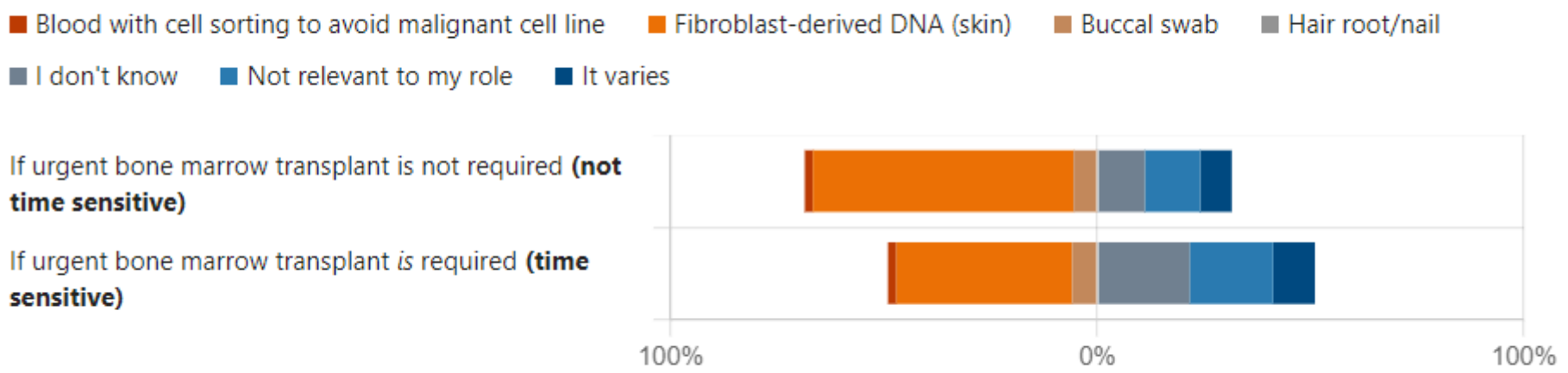
What types of variants should be tested?

Key points:

- **Uncertain: testing moderate risk genes (e.g. *CHEK2)***
- **Uncertain: reporting in an adult for paediatric disorder where phenotype unknown**
- **Uncertain: reporting carrier status if high population frequency (>1/70)**
- **>60% Disagreement: reporting carrier status if low population frequency**



Type of sample used for germline confirmations



Key points: **Lots of comments about use of remission samples**
Practice varies depending on situation

Summary

- Significant variation in practice across the UK currently
- There would be utility in developing guidelines around
  - Types of somatic variants to report
  - The infrastructure for discussing variants prior to reporting/confirmations
  - The clinical pathways for germline confirmations
- There is a strong appetite for the development of a national infrastructure to ensure standardised variant interpretation
- There is a strong appetite for the development of a national infrastructure to ensure on-going data collection to improve clinical management