Germline Predisposition to Haematological Malignancies National Consensus Meeting

Day 1: Lay Person Summary and overview

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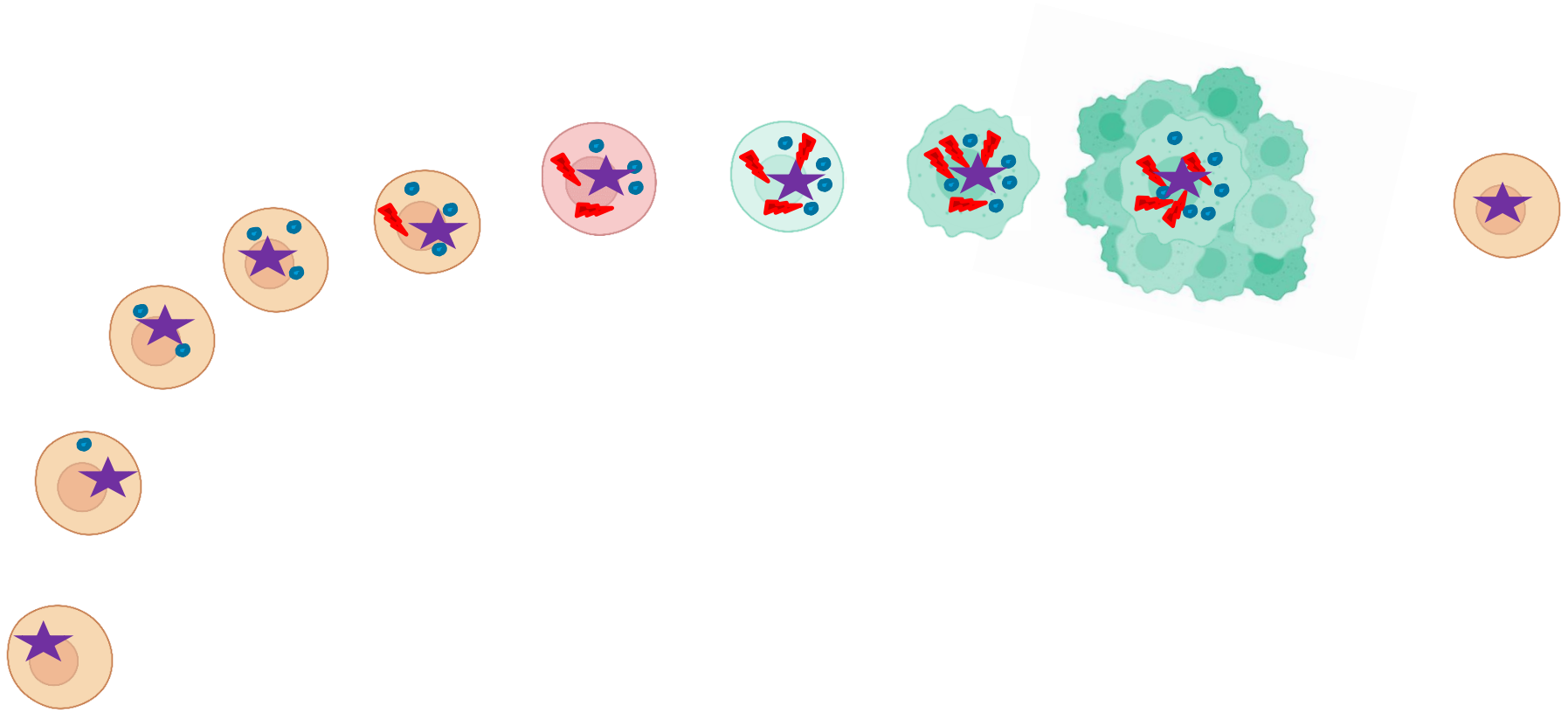
NHS

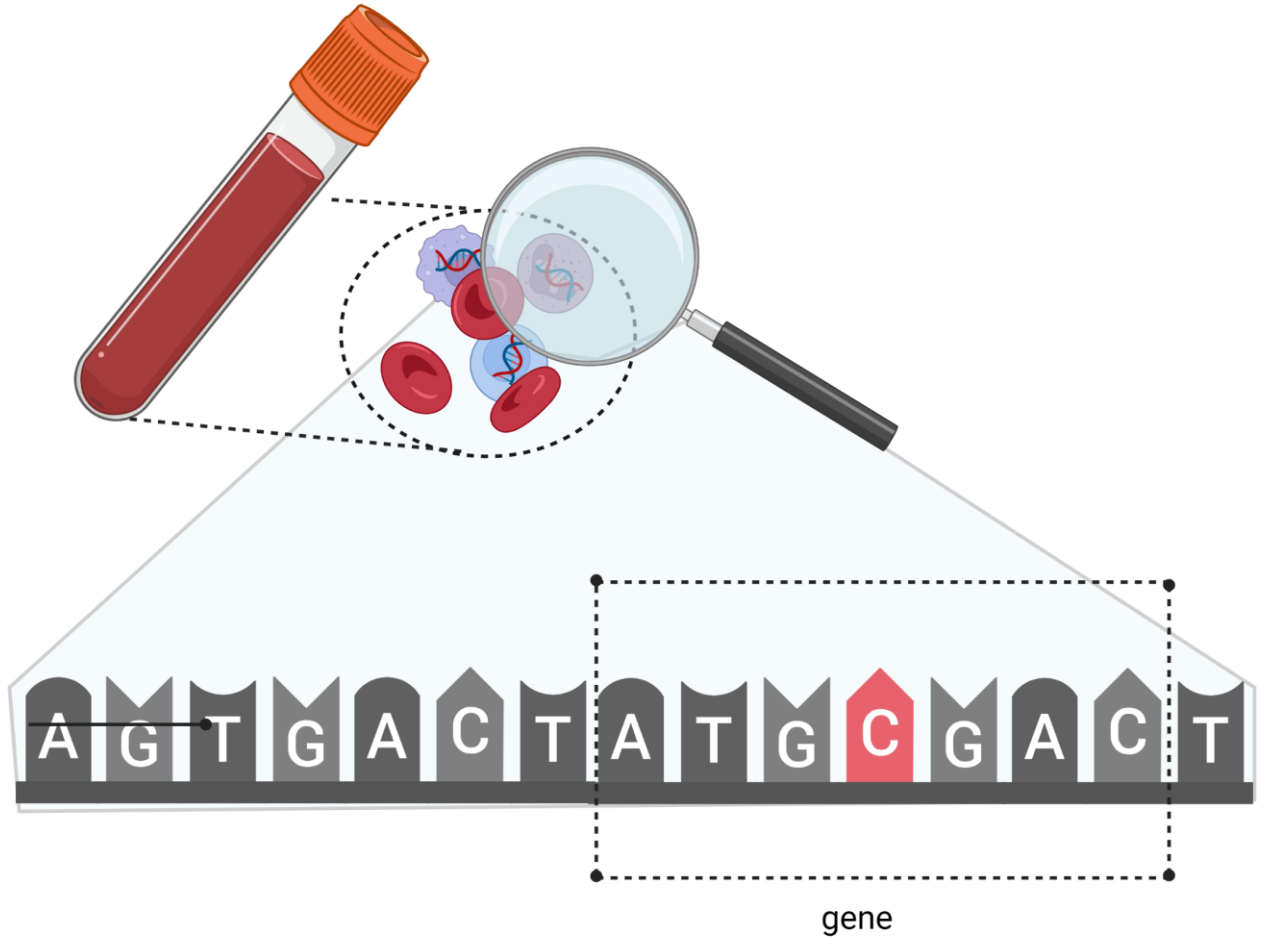
CanGene CanVar

Funded by CANCER RESEARCH UK

GENOMIC CHANGES IN CANCER CELLS



Genetic testing



What types of genetic changes are harmful?

COLOUR

KOOLOUR

Variant of **U**ncertain **S**ignificance

(VUS)

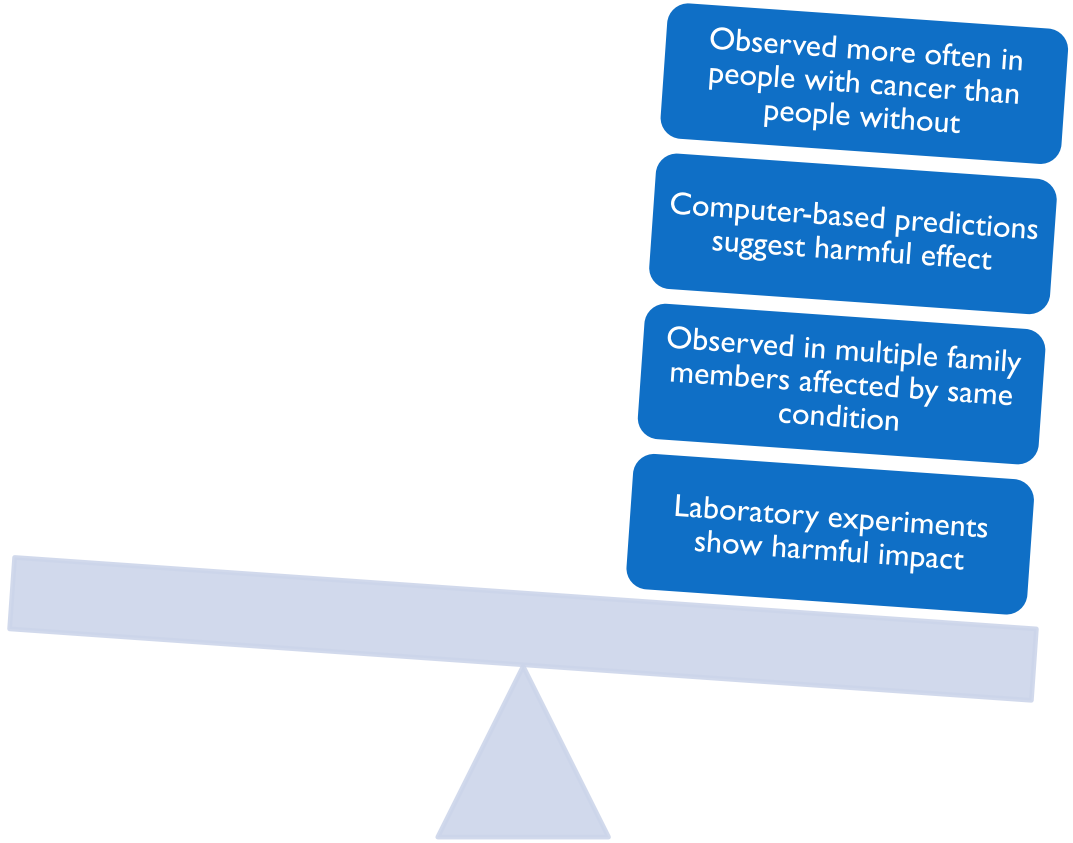
Pathogenic

Benign

Pathogenic

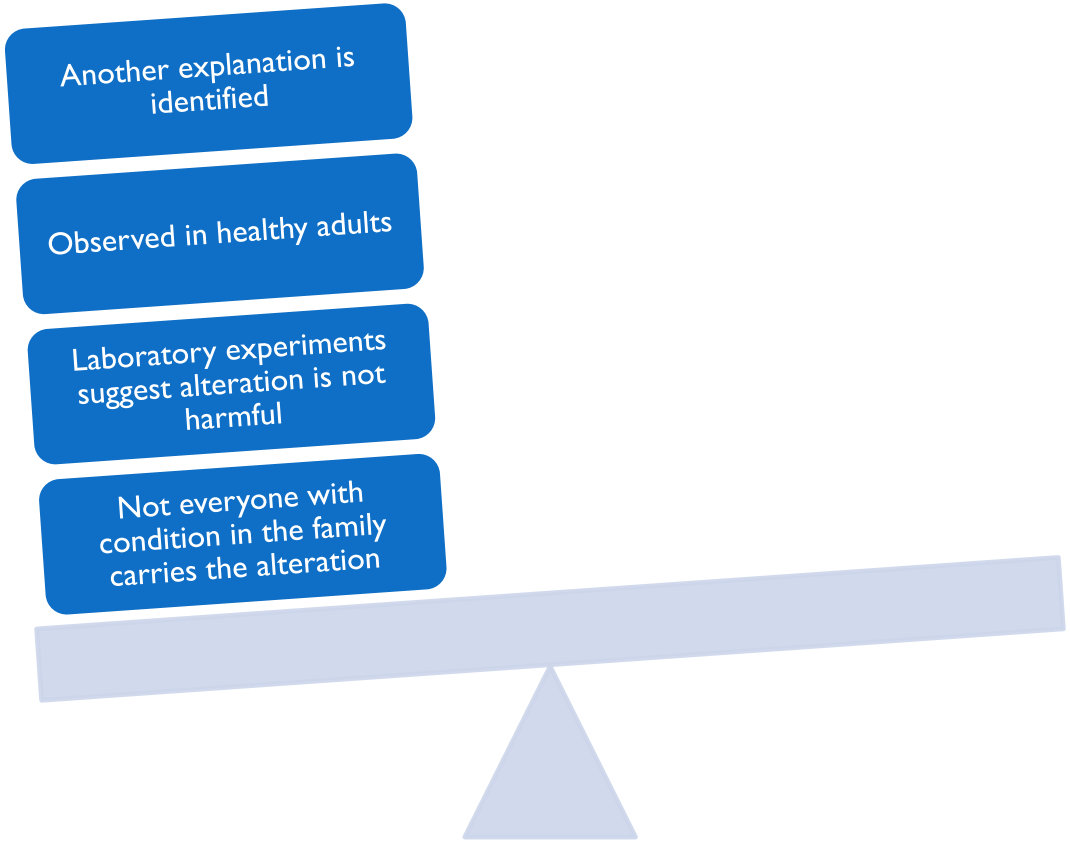
Benign

Pathogenic



Benign

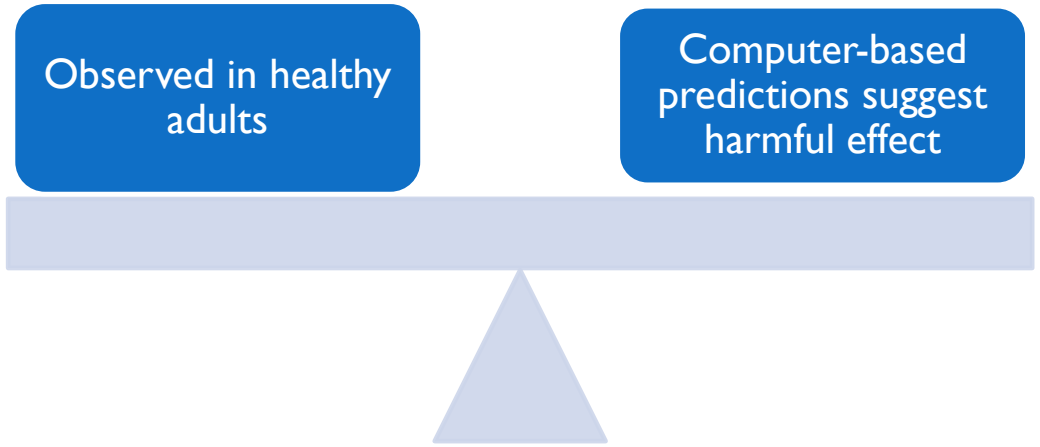
Pathogenic



Benign

Pathogenic

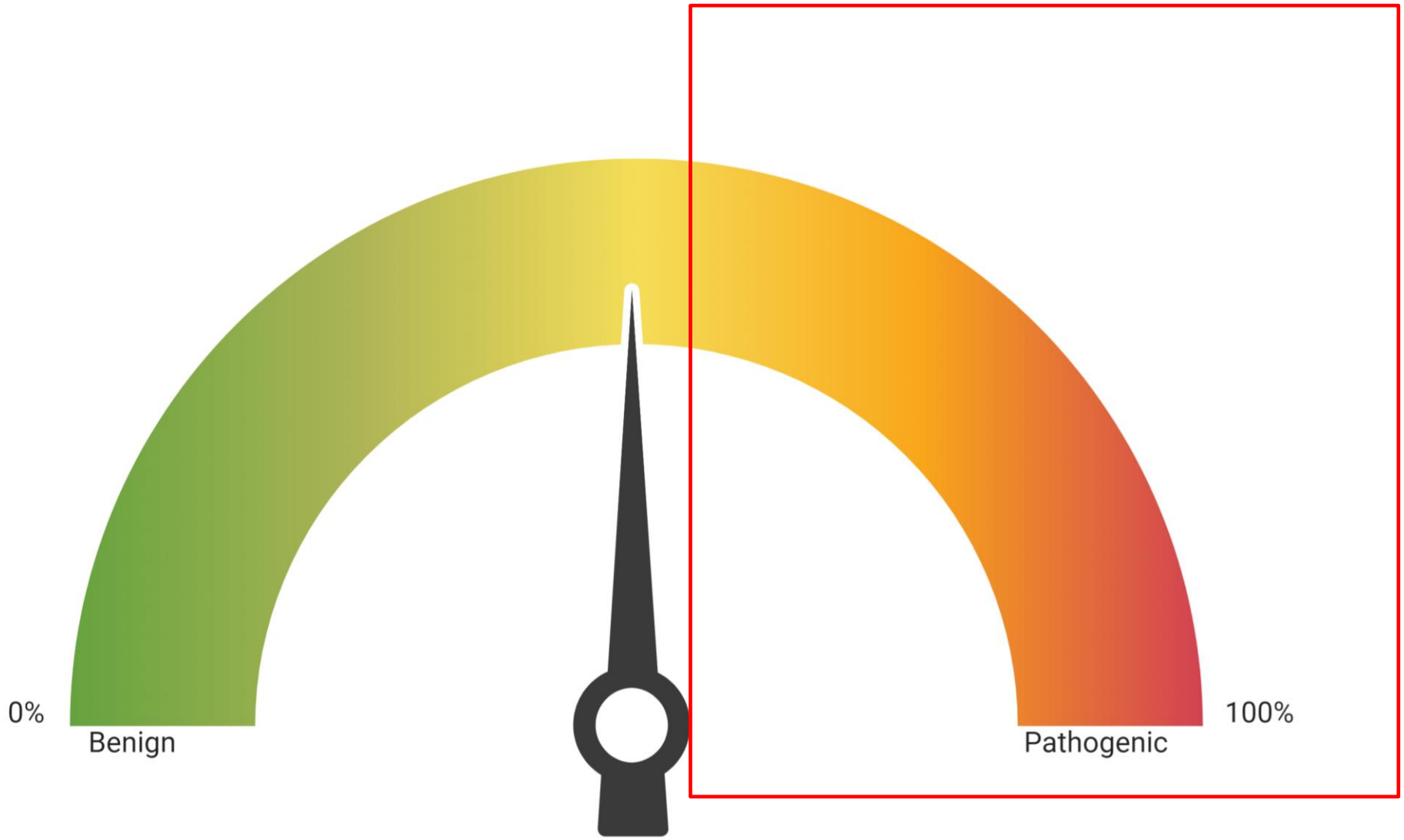
?



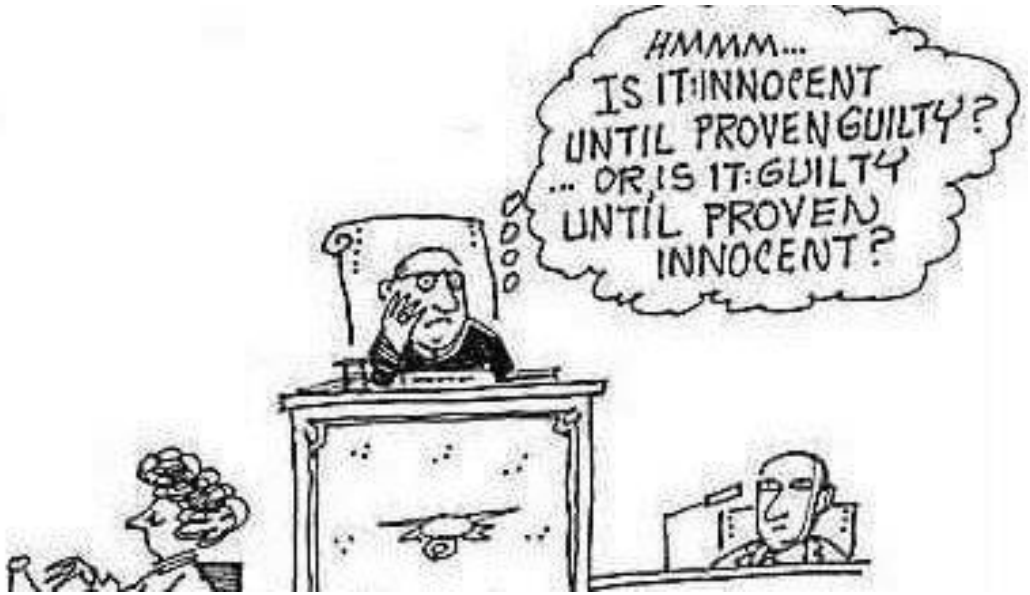
Benign

Pathogenic

?

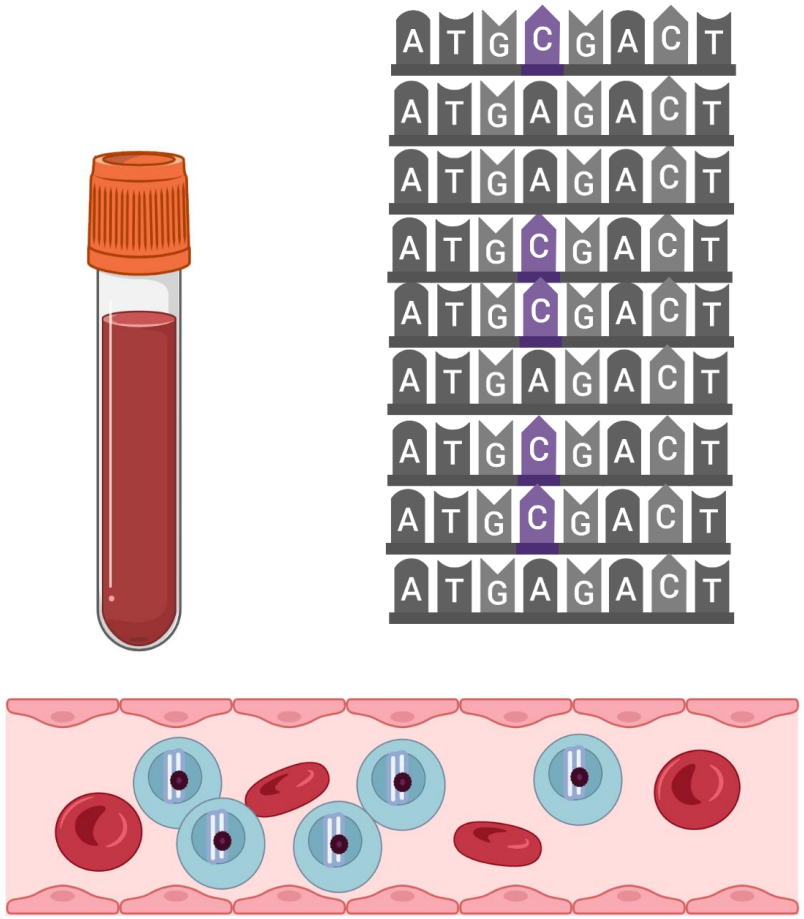

0%
Benign
Pathogenic
100%

What happens if a VUS is identified?



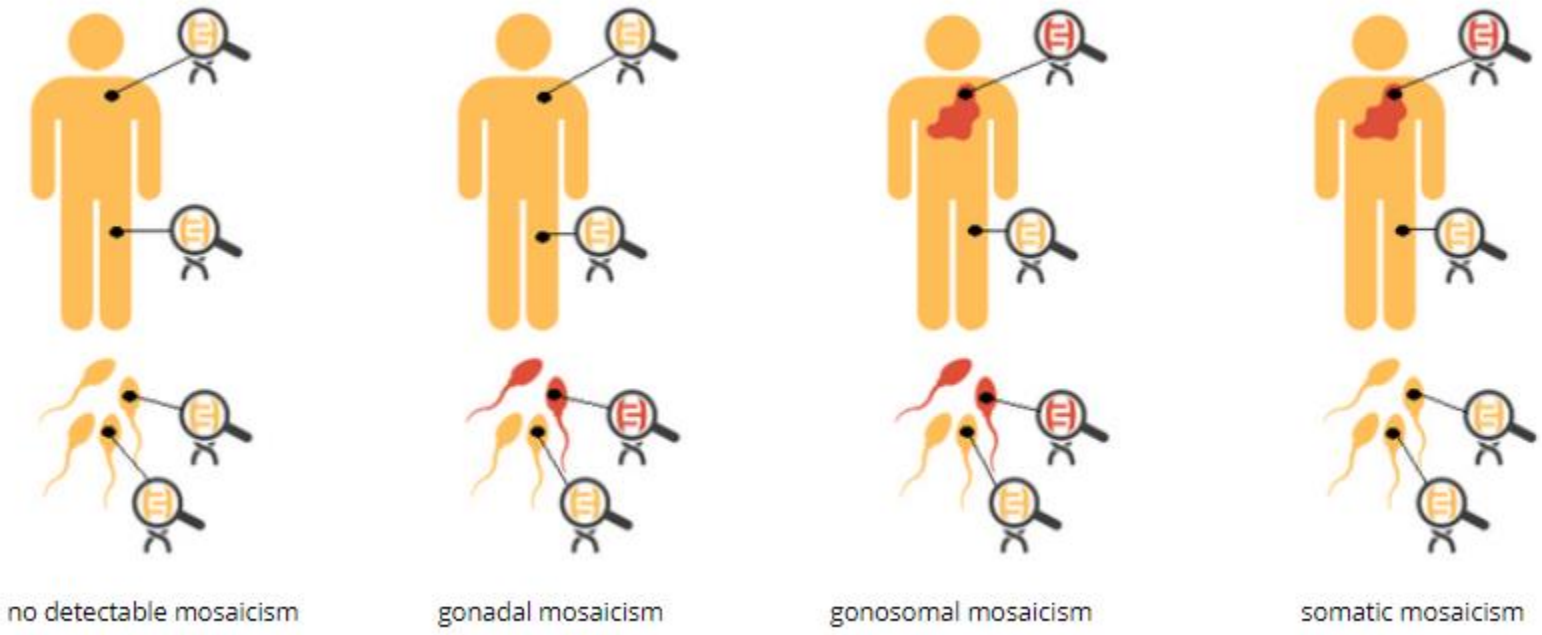
- If a VUS result is identified, management should NOT be based on the genetic result alone
- If VUS incorrectly treated as "guilty" and turns out to be "innocent"…
  - Missed opportunity to use related donor
  - Wrong diagnosis
  - Inappropriate testing in family → false reassurance OR unnecessary anxiety

VAF?



- Heritable alterations in one copy of a gene will be detected in approximately 50% of the "reads" of a genetic test
- BUT genetic alterations happening by chance in blood cancer cells may be present in and around that level too
- Sometimes heritable alterations may not be present at quite so high a level because of other genomic changes in the leukemic cells
- Issues
  - When should we suspect it is heritable?

TYPES OF MOSAICISM



HOW DO WE KNOW IF ALTERATION LIMITED TO LEUKEMIC CELLS??

- Is the alteration present in other (non-blood) cells
  - Skin
  - Hair/nails
  - Non-cancerous blood cells
  - Remission sample

- Which sample is "best" – how do we **avoid contamination**?

CONSENSUS REACHED:

- A statement on the report suggesting possible germline origin should be considered for any variant where a confirmed germline finding would have potential clinical significance, **esp if VAF >30%**
- Variants which are clearly clinically actionable in both the somatic (driver) and germline (Class 4/5 LP/P) setting can be **reported at time of somatic analysis without further discussion**
- Scientists writing somatic reports should ideally **have pre-reporting access to germline scientific/clinical expertise** when deciding if to report putative germline variants which may be VUS on germline classification
- There should be **different template phrases for actionability in different contexts –**
  - to differentiate between variants which are clearly clinically actionable in the germline (Class 4/5 LP/P) and those which may be considered a variant of uncertain significance in the germline

CONSENSUS REACHED:

- Best practice to **perform an assessment of the germline class** of variant according to ACMG/CanVIG-UK/ClinGen guidelines **before the patient is offered confirmatory germline testing** for a somatically identified variant
- 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 all in all situations
- Best practice to **discuss incidental findings with clinical genetics prior to referring patients for confirmatory germline testing**
  - i.e. where an actionable (germline LP/P) variant is identified **NOT causally related** to the clinical phenotype but has clinical implications (e.g. *BRCA1*)

CONSENSUS REACHED:

- For a variant assessed as Class 3 (VUS) in germline, confirmation is not usually indicated. If offered, it would be best practice to have and document an **MDT discussion** about the purpose and utility of confirmatory germline testing before this is offered
  - Particularly pending formal gene-specific variant interpretation guidance
- For a variant assessed as Class 3 (VUS) in germline, confirmation is not usually indicated. If offered, it would be **best practice** to have/document a MDT discussion about rationale for testing relatives esp. if impact on clinical decision making e.g. BMT

CONSENSUS REACHED:

- I would support the development of an accessible forum consisting of both somatic and germline, scientific and clinical expertise for discussion of uncertain/complex/difficult somatic variants which could indicate germline predisposition
- I would support the development of an accessible forum consisting germline scientific and clinical expertise for discussion regarding the management and further work to classify germline variants of uncertain significance

CONSENSUS REACHED:

- I would support providing data on somatic and germline variants to national bodies to enable further research and classification

DISCUSSION ….TBD

- Where germline confirmations are undertaken, the following hierarchy of sample types would be best practice. It is reasonable to move down the list if the first option is deemed clinically inappropriate, impractical or impossible

1. Skin biopsy with cultured fibroblasts
2. Skin biopsy with DNA extraction, not cultured
3. Remission blood
4. Hair root/nail
5. Predictive testing of relatives for a somatically identified variant unconfirmed in the proband where the variant is class 4/5 and at a VAF of >40% if it is time critical to test relative

NB consider gene, **clinical context**, available samples

Remission samples need to be interpreted with caution