Decision tree for nucleotide variant classification and clinical decision making

Sequencing Panel
Whole exome sequencing (WES)
Whole genome sequencing (WGS)

Germline - Somatic

Source/evidence
Reference material (e.g. buccal swab)
Database (e.g. gnomAD)
Variant allele frequency (VAF)

Germline
Familial counseling
Genetic predisposition
Pharmacogenetics
Stem cell transplantation (SCT) family donor

Counseling

Somatic
Identify minimal residual disease (MRD) marker

MRD monitoring

Clinical question

Tier I
Strong clinical significance

Tier II
Potential clinical significance

Tier III
Unknown clinical significance

Tier IV
Benign or likely benign

Pathogenic/driver/actionable
-benign/patient

Source/evidence
FDA-approved therapy
Professional guideline
Studies with consensus from experts
Investigational therapies
Preclinical trials
Case reports
Databases

Diagnosis
Therapy
Prognosis

Baer et al., Haematologica, 2019