Gene table: Considerations for germline testing for variants identified in tumour when VAF is suggestive germline

Gene*	Inheritance pattern Clinical features of a germline pathogenic variant	Molecular features of a germline pathogenic variant	Somatic vs germline vs mosaic	If germline: de novo vs inherited	Resources			Considerations for offering germline testing for identified variant/s
					ACMG V3 2021[1]	eviQ clinically actionable gene list 2022	ESMO Precision Medicine Working Group 2019[2]	
ALK	AD Neuroblastic tumour susceptibility eviQ Clinically actionable gene table	GOF	Variants identified in neuroblastic tumour have a 10% probability of being germline	De novo variants reported Proportion of de novo vs inherited variants is unknown		√		Germline testing is recommended for variants identified in a neuroblastic tumour
APC	AD Familial adenomatous polyposis eviQ Clinically actionable gene table	LOF	Somatic variants very common in colorectal cancer and colorectal polyps Mosaicism reported.	15-20% de novo	√	√	√ Any tumour type with tumour arising under age 30 years only	Germline testing is recommended for variants identified in any tumour type diagnosed under age 30 years Evidence of polyposis may assist in decision to offer germline testing

ATM	AD/(AR) Risk breast and pancreatic cancer (Ataxia telangiectasia) eviQ Clinically actionable gene table	LOF	Germline variants common in population	Usually inherited rather than de novo		√	>10% probability germline but excluded from list as moderate penetrance gene without broad consensus re: risk management	c.7271T>G likely to be germline and is clinically actionable. Germline testing recommended Clinical utility of germline testing for other pathogenic variants may vary depending on personal/family history and reproductive considerations Counselling should include reproductive implications Facts for people from a family with a faulty ATM gene who are planning a pregnancy
BAP1	AD BAP1 tumour predisposition syndrome eviQ Clinically actionable gene table	LOF	Based on IHC results, biallelic somatic variants common in mesothelioma, renal cancer and metastatic melanoma	De novo rate unknown but reported		√	√ Associated tumour only	Germline testing to be considered for variants identified in BAP1-related tumour Additional personal/family history BAP1-associated tumours may assist in decision to offer germline testing.
BARD1	AD Moderate risk breast cancer eviQ Clinically actionable gene table (pending)	LOF				√ (pending)		Clinical utility of identifying a germline variant outside of a personal/close family history of breast cancer is uncertain

BMPR1A	AD Juvenile polyposis syndrome eviQ Clinically actionable gene table	LOF	Detected variants more likely to be somatic than germline	Around 25% de novo	√	√		Clinical history of juvenile polyposis may assist in decision to offer germline testing.
BRCA1	AD Hereditary breast/ovarian cancer eviQ Clinically actionable gene table	LOF 2nd hit in associated tumours	Detected variants more likely to be germline than somatic in any tumour type	De novo variants rare	√	√	√ Any tumour Any age	Due to: Probability (but not certainty) of an identified variant being germline AND high potential clinical actionability **germline testing is recommended for variants identified in any tumour type at any age regardless of personal/family history**

BRCA2	AD Hereditary breast/ovarian cancer eviQ Clinically actionable gene table	LOF 2nd hit in associated tumours	Detected variants more likely to be germline than somatic in any tumour type	De novo variants rare	√	√	√ Any tumour Any age	Due to: Probability (but not certainty) of an identified variant being germline AND high potential clinical actionability **germline testing is recommended for variants identified in any tumour type at any age regardless of personal/family history**
BRIP1	AD Moderate risk ovarian cancer eviQ Clinically actionable gene table	LOF	Detected variants more likely to be germline than somatic in any tumour type			√	√ Any tumour Any age	Ovarian cancer risk clinically actionable for female patient/relatives regardless of personal/family history Germline testing recommended for variants identified in any tumour type at any age
CDC73	AD Hyperparathyroidism jaw tumour syndrome eviQ Clinically actionable gene table	LOF		De novo rate unknown		√		Review on a case-by-case basis taking personal/family history into consideration

CDH1	AD Hereditary diffuse gastric cancer eviQ Clinically actionable gene table	LOF	Somatic variants common in diffuse gastric and lobular breast cancer	De novo variant rate unknown but low		√		Limited data available to guide strategy Highest probability of variant being germline and clinical utility of confirming this is in individuals who fulfill eviQ CDH1 genetic testing guidelines Cancer risks are uncertain for germline variants ascertained outside the setting of diffuse gastric cancer or lobular breast cancer Pre-test counselling by a familial cancer service is recommended if considering germline testing
CDKN2A	AD Risk melanoma and pancreatic cancer eviQ Clinically actionable gene table	LOF		De novo variants rare		√		Limited clinical utility of confirming germline variant outside the setting of a personal/family history of melanoma or pancreatic cancer

CHEK2	AD Moderate risk breast cancer eviQ Clinically actionable gene table	LOF				√	>10% probability germline but excluded from list as moderate penetrance gene without consensus re: risk management	Clinical utility of germline testing for pathogenic variants may vary depending on personal/family history
DICER1	AD DICER1 syndrome eviQ Clinically actionable gene table	LOF		Usually inherited		√		Germline testing should be considered for variants identified in DICER1-related tumour
EPCAM	AD Lynch syndrome eviQ Clinically actionable gene table	Deletion 3' end EPCAM leading to epigenetic silencing of MSH2				√		Consider germline testing for 3' deletion regardless of tumour type
FH	AD Hereditary leiomyosis and renal cell carcinoma eviQ Clinically actionable gene table	LOF		De novo rate unknown		√	√ Associated tumour only	Consider germline testing regardless of tumour type

FLCN	AD Birt-Hogg-Dubé syndrome eviQ Clinically actionable gene table	LOF				√	√ Associated tumour only	Consider germline testing regardless of tumour type
HOXB13	AD Risk of prostate cancer eviQ Clinically actionable gene table			G84E variants likely to be inherited		√ G84E only	>10% probability germline but excluded from list as moderate penetrance gene without consensus re: risk management	G84E likely to be germline Discuss germline testing if ascertained in the context of a personal and/or family history of prostate cancer
LZTR1	AD Schwannomatosis eviQ Clinically actionable gene table	LOF	Associated tumours typically have with 4-5 hit mechanism involving NF2 +/- SMARCB1 Mechanism underlying LZTR1, SMARCB1 and NF2-related schwannomatosis			√		Germline testing recommended for variants identified in a related tumour

MAX	AD Hereditary paraganglioma-phaeochromocytoma syndrome	LOF		De novo rate unknown	√			Limited penetrance data limits usefulness when detected in unrelated tumours
MEN1	AD Multiple endocrine neoplasia type1 eviQ Clinically actionable gene table	LOF		Around 10% de novo	√	√		Review on a case-by-case basis taking personal/family history into consideration
MET	AD Hereditary papillary renal cell carcinoma type 1 eviQ Clinically actionable gene table	GOF				√		Review on a case-by-case basis taking personal/family history into consideration

MLH1	AD Lynch syndrome eviQ Clinically actionable gene table	LOF	Detected sequence variants in any tumour type have a >10% probability of being germline	De novo variants rare	√	√	√ Any tumour Any age	Due to: Probability (but not certainty) of an identified variant being germline AND high potential clinical actionability **germline testing is recommended for variants identified in any tumour type at any age regardless of personal/family history**
MSH2	AD Lynch syndrome eviQ Clinically actionable gene table	LOF	Detected sequence variants in any tumour type have a >10% probability of being germline	De novo variants rare	√	√	√ Any tumour Any age	Due to: Probability (but not certainty) of an identified variant being germline AND high potential clinical actionability **germline testing is recommended for variants identified in any tumour type at any age regardless of personal/family history**

MSH6	AD Lynch syndrome eviQ Clinically actionable gene table	LOF	Detected sequence variants in any tumour type have a >10% probability of being germline	De novo variants rare	√	√	√ Any tumour Any age	Due to: Probability (but not certainty) of an identified variant being germline AND high potential clinical actionability **germline testing is recommended for variants identified in any tumour type at any age regardless of personal/family history**
MUTYH	AR MUTYH-associated polyposis eviQ Clinically actionable gene table	LOF	Germline variants common in population (around 1/45)		√ (2 variants only)	√ (biallelic variants)	√ Any tumour Any age 2 variants only	Recommend germline testing only when two variants identified in tumour
NF1	AD Neurofibromatosis type 1 eviQ Clinically actionable gene table	LOF	Somatic variants common Mosaicism reported	Almost 50% de novo		√	√ Associated tumour arising under age 30 years only	Recommend germline testing if identified in an associated tumour diagnosed under age 30 years Clinical examination for associated phenotypic features (e.g. café au lait macules, neurofibromas) may assist in decision to offer germline testing

NF2	AD Neurofibromatosis type 2 eviQ Clinically actionable gene table	LOF	Mosaicism well described Somatic NF2 variants can be associated with germline and somatic SMARCB1 and LZTR1 variants in associated tumours Mechanism underlying LZTR1, SMARCB1 and NF2-related schwannomatosis	Around 50% de novo	√	√		Review whether germline testing for the identified variant/s should be offered on a case-by-case basis taking personal/family history into consideration If detected in a SMARCB1/LZTR1 associated tumour, consider whether germline testing of these genes should also be considered
PALB2	AD Hereditary breast/ovarian cancer eviQ Clinically actionable gene table	LOF	Detected variants more likely to be germline than somatic in any tumour type		√	√	√ Any tumour Any age	Due to: Probability (but not certainty) of an identified variant being germline AND high potential clinical actionability **germline testing is recommended for variants identified in any tumour type at any age regardless of personal/family history**

PMS2	AD Lynch syndrome eviQ Clinically actionable gene table	LOF	Detected variants more likely to be germline than somatic in any tumour type	De novo variants rare	√	√	√ Any tumour Any age	Due to: Probability (but not certainty) of an identified variant being germline AND high potential clinical actionability **germline testing is recommended for variants identified in any tumour type at any age regardless of personal/family history**
POLD1	AD Polymerase proof-reading polyposis eviQ Clinically actionable gene table	GOF		De novo rate unknown		√		Germline testing recommended for specific variants identified in a related tumour
POLE	AD Polymerase proof-reading polyposis eviQ Clinically actionable gene table	GOF		De novo variants described but rate unknown		√	√ Associated tumour only	Germline testing recommended for specific variants identified in a related tumour

PTCH1	AD Gorlin syndrome eviQ Clinically actionable gene table	LOF		20-30% de novo		√		Clinical examination for associated phenotypic features may assist in decision to offer germline testing
PTEN	AD Cowden syndrome eviQ Clinically actionable gene table	LOF	Somatic variants are common	De novo rate unknown	√	√		Clinical examination for associated phenotypic features may assist in decision to offer germline testing
RAD51C	AD Moderate risk ovarian cancer and increased risk breast cancer eviQ Clinically actionable gene table	LOF	Detected variants more likely to be germline than somatic in any tumour type	Usually inherited		√	√ Any tumour Any age	Ovarian cancer risk clinically actionable for female patient/relatives regardless of personal/family history Germline testing recommended for variants identified in any tumour type at any age
RAD51D	AD Moderate risk ovarian cancer and increased risk breast cancer eviQ Clinically actionable gene table	LOF	Detected variants more likely to be germline than somatic in any tumour type	Usually inherited		√	√ Any tumour Any age	Ovarian cancer risk clinically actionable for female patient/relatives regardless of personal/family history Germline testing recommended for variants identified in any tumour type at any age

RB1	AD Retinoblastoma eviQ Clinically actionable gene table	LOF	Somatic variants common Mosaicism well described		√	√	√ Any tumour type with tumour arising under age 30 years only	Germline testing is recommended for variants identified in tumours of any type diagnosed under age 30 years Consider testing of older individuals if there is a related personal/family history of cancer
RET	AD Multiple endocrine neoplasia type 2 eviQ Clinically actionable gene table	GOF		De novo rate varies (5% MEN2A and 75% MEN2B)	√	√	√ Any tumour Any age	Due to: Probability (but not certainty) of an identified variant being germline AND high potential clinical actionability **germline testing is recommended for GOF variants identified in any tumour type at any age regardless of personal/family history**

SDHA	AD Hereditary paraganglioma-phaeochromocytoma syndrome eviQ Clinically actionable gene table	LOF	Detected variants more likely to be germline than somatic in any tumour type	De novo variants described but rate unknown Most inherited		√	√ Any tumour Any age	Low penetrance limits usefulness when detected in unrelated tumours
SDHAF2	AD with parent of origin effect Hereditary paraganglioma-phaeochromocytoma syndrome eviQ Clinically actionable gene table	LOF	Detected variants more likely to be germline than somatic in any tumour type	De novo rate unknown	√	√	√ Any tumour Any age	Limited penetrance data available Review on a case-by-case basis taking personal/family history into consideration

SDHB	AD Hereditary paraganglioma-phaeochromocytoma syndrome eviQ Clinically actionable gene table	LOF	Detected variants more likely to be germline than somatic in any tumour type	De novo variants described but rate unknown Most inherited	√	√	√ Any tumour Any age	Due to: Probability (but not certainty) of an identified variant being germline AND high potential clinical actionability **germline testing is recommended for variants identified in any tumour type at any age regardless of personal/family history**
SDHC	AD Hereditary paraganglioma-phaeochromocytoma syndrome eviQ Clinically actionable gene table	LOF	Detected variants more likely to be germline than somatic in any tumour type	De novo variants described but rate unknown Most inherited	√	√	√ Any tumour Any age	Germline testing recommended for variants identified in any tumour type at any age
SDHD	AD with parent of origin effect Hereditary paraganglioma-phaeochromocytoma syndrome eviQ Clinically actionable gene table	LOF	Detected variants more likely to be germline than somatic in any tumour type	De novo variants described but rate unknown Most inherited	√	√	√ Any tumour Any age	Germline testing recommended for variants identified in any tumour type at any age.

SMAD4	AD Juvenile polyposis syndrome Hereditary haemorrhagic telangiectasia (HHT) eviQ Clinically actionable gene table	LOF	Somatic variants common	Around 25% de novo	√	√		Clinical history of juvenile polyposis and/or HHT may assist in decision to validate
SMARCA4	AD Rhabdoid tumour predisposition syndrome (RTPS) eviQ Clinically actionable gene table	LOF		Most variants associated with RTPS are de novo		√		Germline testing recommended for variants identified in a related tumour
SMARCB1	AD Rhabdoid tumour predisposition syndrome (RTPS) Schwannomatosis eviQ Clinically actionable gene table	LOF	Associated tumours typically have with 4-5 hit mechanism involving NF2 +/- LZTR1 Mechanism underlying LZTR1, SMARCB1 and NF2-related schwannomatosis	Most variants associated with RTPS are de novo		√		Germline testing recommended for variants identified in a related tumour

STK11	AD Peutz-Jeghers syndrome eviQ Clinically actionable gene table	LOF	Somatic variants common and well recognised in lung adenocarcinoma	Up to 50% de novo	√	√		Clinical examination recommended for associated phenotypic features to guide decision to validate
SUFU	AD Gorlin syndrome eviQ Clinically actionable gene table	LOF				√		Insufficient data on which to base recommendation Review on a case-by-case basis taking personal/family history into consideration
TMEM127	AD Hereditary paraganglioma-phaeochromocytoma syndrome	LOF		De novo rate unknown	√			Limited penetrance data limits usefulness when detected in unrelated tumours
TP53	AD Li Fraumeni syndrome eviQ Clinically actionable gene table	LOF	Most commonly mutated gene across all cancer types Detected variants much more likely to be somatic than germline in any tumour type	Overall, around 14% de novo but varies with tumour type	√	√	√ Associated tumour arising under age 30 years only (excluding brain tumours)	Germline testing is recommended for variants identified in tumours of any type (except brain tumour) diagnosed under age 30 years

TSC1	AD Tuberous sclerosis complex eviQ Clinically actionable gene table	LOF	Identified variants usually somatic Mosaicism well described		√	√ (Risk management guidelines out of scope)		Review on a case-by-case basis taking personal/family history into consideration
TSC2	AD Tuberous sclerosis complex eviQ Clinically actionable gene table	LOF	Mosaicism well described		√	√ (Risk management guidelines out of scope)	√ Any tumour Any age	Germline testing recommended for variants identified in any tumour type at any age
VHL	AD Von Hippel-Lindau syndrome eviQ Clinically actionable gene table	LOF	Somatic variants very common in clear cell renal cell carcinoma Mosaicism well described	Around 20% de novo	√	√	√ Any tumour (except renal cancer) Any age	Germline testing recommended for variants identified in any tumour type (except renal cancer) at any age
WT1	AD WT1-related Wilms tumour	LOF			√			Review on a case-by-case basis taking personal/family history into consideration

Abbreviations: AD: Autosomal dominant, AR: Autosomal recessive, GOF: Gain of function, IHC: immunohistochemistry, LOF: loss of function, VAF: variant allele frequency

Genes associated with both high clinical utility and >10% probability germline, regardless of tumour type the variant is identified in.

**Where data has been derived from another eviQ document, the original reference has not been re-cited in this document*

References:

1. Miller, D. T., K. Lee, W. K. Chung, et al. 2021. "ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG)." Genet Med 23(8): 1381-1390.
2. Mandelker, D., M. Donoghue, S. Talukdar, et al. 2019. "Germline-focussed analysis of tumour-only sequencing: recommendations from the ESMO Precision Medicine Working Group." Ann Oncol 30(8): 1221-1231

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