

A Single Institution Review of Frequency of Potential Germline Mutations in ctDNA Testing in Advanced Lung Cancer Patients and Referral Patterns to Clinical Genetics



John Michael Miro, Tracy L. Stockley, Frances A. Shepherd, Penelope A. Bradbury, Geoffrey Liu, Adrian G. Sacher, Lawson Eng, Jessica Danquah, Tong Zhang, Lisa W. Le, Janice J.N. Li, Amina Ahmed, Mary R. Rabey, Yashvi Verma, Natasha B. Leighl
Correspondence: Natasha.Leighl@uhn.ca

IASLC 2026 World
Conference on Lung Cancer
SEPTEMBER 12 – 15, 2026
SEOUL, REPUBLIC OF KOREA

INTRODUCTION

- Approximately 0.3% to 7% of patients with lung cancer may harbor a pathogenic germline mutation.
- Pathogenic (P)/likely pathogenic (LP) germline variants (PGVs) appear to increase the risk of developing lung cancer.
- There is an 18% risk in patients with a positive family history of lung cancer.
- While current guidelines recommend referral of appropriate patients to assess germline risk based on somatic molecular test results, there is a lack of awareness as to which results should trigger referral.
- We conducted a single institution study to assess referral rates for patients with lung cancer and somatic variants identified in plasma circulating tumor DNA (ctDNA) for germline mutation testing.

METHODS

Genes screened for germline-focused analysis and follow-up				
Any age	ATM BAP1 BARD1 BRCA1 BRCA2 BRIP1 CHEK2 DICER1 FH	FLCN MLH1 MSH2 MSH6 MUTYH NF1 PALB2 PTCH1 PMS2	RAD51C RAD51D POLD1 POLE RET SDHA SDHAF2 SDHB	SDHC SDHD SMAD3 SMARCB1 SUFU TMEM127 TSC2 VHL
<30 years old	APC SMARCA4	CDKN2A TP53	PTEN	RB1
Cutoffs: - Tumour-observed VAF >30% for SNVs or - Tumour-observed VAF >20% for small insertions/deletions.				

Design:

- Sequencing data from 522 lung cancer patients who underwent plasma ctDNA somatic mutation profiling for treatment selection between 2019 and 2024 were reviewed.
- Using the ESMO Precision Medicine Working Group's recommendations for referral for germline testing [reference], patients with potential pathogenic or likely pathogenic germline mutations were identified. Genomics results were correlated with available data from the ClinVar database (National Center for Biotechnology Information, NCBI) and the University Health Network (UHN) Advanced Molecular Diagnostics Laboratory, and confirmed with the clinical genetics team at UHN.
- Referral rates to the clinical genetics service for germline testing and subsequent confirmation of PGVs were recorded.

DISCUSSION AND CONCLUSION

- In patients with plasma ctDNA genotyping as part of lung cancer diagnosis, the frequency of germline mutations was low but significant.
- The ESMO Precision Working Group's recommendations for flagging potential germline variants, and review of somatic variants for germline pathogenicity, provide a high-yield filter for germline confirmation, as 4 of 5 cases that were referred to genetics had confirmed germline variants.
- This study also reveals the low rates of recognition by providers and referral of patients with potential pathogenic germline mutations for hereditary genetic assessment.
- As somatic testing increases in lung and other cancers, this study highlights the unmet need for increased awareness and education on the appropriate identification and referral of patients at risk of pathogenic germline mutations.
- Active collaboration between clinicians, pathologists, and genetics specialists is key to further improving outcomes in the management of lung cancer moving forward.
- However, a limitation of this study is that not all of the somatic mutation profiling reports were clinical grade, and some germline mutations may not have been flagged because of this.

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RESULTS

Of 522 patients, 15 (3%) had potential pathogenic germline mutations detected on plasma ctDNA testing. Five (33%) were referred to genetics service for consideration of germline testing; 4 had germline variants identified and in 1 patient, a germline variant was not confirmed.

Clinical and Genomic Information for Patients Harboring Pathogenic/Likely Pathogenic Mutations								
Patient No.	Age	Sex	Mutation	Protein	Histology	Variant germline classification	Genetics referral?	Germline Genetic Testing
P1	77F		MUTYH c.1178G>A	p.Gly393Asp	Adenocarcinoma	Pathogenic	N	Not done
P2	50F		BRCA2 c.930_931del	p.Cys311PhefsTer3	Adenocarcinoma	Pathogenic	N	Not done
P3	66F		DICER1 c.4405_4406del	p.Leu1469PhefsTer7	Adenocarcinoma	Pathogenic	Y	Germline VUS SHDA c1177G>T p.(Val.393Leu) mutation. Germline DICER1 mutation not confirmed in germline testing.
P4	73M		PALB2 c.2267_2283dup	p.His762Alafs*8	Adenocarcinoma	Likely pathogenic	N	Not done
P5	63M		NF1 c.7884_7900del	p.Lys2628AsnfsTer2	Adenocarcinoma	Pathogenic	N	Not done
P6	62M		BRCA1 c.4186-1G>T	p.?	Adenocarcinoma	Likely pathogenic	Y	Germline VUS BRCA1 c.4186-1G>T mutation.
P7	25M		ATM c.8873_8874del	p.Phe2958Ter	Adenocarcinoma	Likely pathogenic	Y	Pathogenic germline ATM c.8873_8874delTT, p.(Phe2958Ter) mutation.
P8	22M		TP53 c.825_832delinsAGGTG	p.Cys275Ter	Adenocarcinoma	Likely pathogenic	Y	Pathogenic germline TP53 p.C275Ter mutation.
P9	73M		EGFR c.2369C>T	p.Thr790Met	Adenocarcinoma	Pathogenic	N	Not done.
P10	68M		NF1 c.4930G>C	p.Asp1644His	Adenocarcinoma	Likely pathogenic	N	Not done.
P11	55F		NF1 c.3337delC	p.Leu1113fs	Sarcomatoid	Likely pathogenic	N	Not done.
P12	29M		TP53 c.341delT	p.Leu114CysfsTer9	Adenocarcinoma	Likely pathogenic	N	Not done.
P13	85F		PALB2 c.395delT	p.Val132AlafsTer45	Adenocarcinoma	Likely pathogenic	N	Not done.
P14	54F		ATM c.748C>T	p.Arg250Ter	Adenocarcinoma	Pathogenic	N	Not done.
P15	53F		BRCA2 c.9235del	p.V3079fs	Adenocarcinoma	Likely pathogenic	Y	Pathogenic germline BRCA2 c.9235del, a nonsense mutation that results in p.V3079fs.