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Circulating Tumour DNA Testing for the Identification of Genetic Mutations: Diagnostic Test Accuracy and Clinical Utility

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Research Questions

1. What is the diagnostic test accuracy of circulating tumour DNA testing for the identification of genetic mutations?
2. What is the clinical utility of circulating tumour DNA testing for the identification of genetic mutations?
3. What is the cost-effectiveness of circulating tumour DNA testing for the identification of genetic mutations?

Key Findings

Four systematic reviews and meta-analyses, three randomized controlled trials, and 44 non-randomized studies were identified regarding the diagnostic test accuracy and clinical utility of circulating tumour DNA testing for the identification of genetic mutations.

Methods

A limited literature search was conducted by an information specialist on key resources including Medline via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were circulating tumour DNA and specific biomarkers. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, network meta-analyses, any types of clinical trials or observational studies, economic studies, and diagnostic test accuracy studies. The search was also limited to English language documents published between Jan 1, 2015 and Jan 7, 2020. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	People diagnosed with cancer who require biomarker testing prior to targeted drug therapy
Intervention	Circulating tumour DNA (ctDNA) testing - alone or as part of a panel Specifically interested in the following biomarkers: - ALK - EGFR - BRAF V600E - ROS1 - BRCA-1 / BRCA-2 - KIT
Comparator	Pathology-based testing
Outcomes	Diagnostic test accuracy, clinical utility, cost-effectiveness
Study Designs	Health technology assessments, systematic reviews, randomized control trials, non-randomized studies, economic evaluations.

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and economic evaluations, and evidence-based guidelines.

Four systematic reviews and meta-analyses,[1-4] three randomized controlled trials,[5-7] and 44 non-randomized studies[8-51] were identified regarding the diagnostic test accuracy and clinical utility of circulating tumour DNA testing for the identification of genetic mutations.

Additional references of potential interest are provided in the appendix.

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

EGFR Biomarker Related Studies

1. Passiglia F, Rizzo S, Di Maio M, et al. The diagnostic accuracy of circulating tumor DNA for the detection of EGFR-T790M mutation in NSCLC: a systematic review and meta-analysis. *Sci*. 2018 09 06;8(1):13379.
PubMed: PM30190486

2. Passiglia F, Rizzo S, Rolfo C, et al. Metastatic Site Location Influences the Diagnostic Accuracy of ctDNA EGFR- Mutation Testing in NSCLC Patients: a Pooled Analysis. *Curr Cancer Drug Targets*. 2018;18(7):697-705.
PubMed: PM29521235

3. Zhang R, Chen B, Tong X, et al. Diagnostic accuracy of droplet digital PCR for detection of EGFR T790M mutation in circulating tumor DNA. *Cancer Manag Res*. 2018;10:1209-1218.
PubMed: PM29844700

4. Qiu M, Wang J, Xu Y, et al. Circulating tumor DNA is effective for the detection of EGFR mutation in non-small cell lung cancer: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2015 Jan;24(1):206-212.
PubMed: PM25339418

Randomized Controlled Trials

EGFR Biomarker Related Studies

5. Gray JE, Okamoto I, Sriuranpong V, et al. Tissue and Plasma EGFR Mutation Analysis in the FLAURA Trial: Osimertinib versus Comparator EGFR Tyrosine Kinase Inhibitor as First-Line Treatment in Patients with EGFR-Mutated Advanced Non-Small Cell Lung Cancer. *Clin Cancer Res*. 2019 Nov 15;25(22):6644-6652.
PubMed: PM31439584

6. Mok T, Wu YL, Lee JS, et al. Detection and Dynamic Changes of EGFR Mutations from Circulating Tumor DNA as a Predictor of Survival Outcomes in NSCLC Patients Treated with First-line Intercalated Erlotinib and Chemotherapy. *Clin Cancer Res*. 2015 Jul 15;21(14):3196-3203.
PubMed: PM25829397

BRAF Biomarker Related Studies

7. Sclafani F, Chau I, Cunningham D, et al. KRAS and BRAF mutations in circulating tumour DNA from locally advanced rectal cancer. *Sci*. 2018 01 23;8(1):1445.
PubMed: PM29362371

Non-Randomized Studies

ALK Biomarker Related Studies

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PubMed: PM31444835

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PubMed: PM29376144

EGFR Biomarker Related Studies

10. Merinda V, Soegiarto G, Wulandari L. T790M mutations identified by circulating tumor DNA test in lung adenocarcinoma patients who progressed on first-line epidermal growth factor receptor-tyrosine kinase inhibitors. *Lung India*. 2020 Jan-Feb;37(1):13-18.
PubMed: PM31898615

11. Denis MG, Lafourcade MP, Le Garff G, et al. Circulating free tumor-derived DNA to detect EGFR mutations in patients with advanced NSCLC: French subset analysis of the ASSESS study. *J*. 2019 Apr;11(4):1370-1378.
PubMed: PM31179079

12. Ding PN, Becker T, Bray V, et al. Plasma next generation sequencing and droplet digital PCR-based detection of epidermal growth factor receptor (EGFR) mutations in patients with advanced lung cancer treated with subsequent-line osimertinib. *Thorac Cancer*. 2019 Oct;10(10):1879-1884.
PubMed: PM31414729

13. Ding PN, Becker TM, Bray VJ, et al. The predictive and prognostic significance of liquid biopsy in advanced epidermal growth factor receptor-mutated non-small cell lung cancer: A prospective study. *Lung Cancer*. 2019 Aug;134:187-193.
PubMed: PM31319980

14. Francaviglia I, Magliacane G, Lazzari C, et al. Identification and monitoring of somatic mutations in circulating cell-free tumor DNA in lung cancer patients. *Lung Cancer*. 2019 Aug;134:225-232.
PubMed: PM31319985

15. Hung MS, Lung JH, Lin YC, et al. Comparative Analysis of Two Methods for the Detection of EGFR Mutations in Plasma Circulating Tumor DNA from Lung Adenocarcinoma Patients. *Cancers (Basel)*. 2019 Jun 10;11(6):10.
PubMed: PM31185703

16. Li Y, Xu Y, Wu X, He C, Liu Q, Wang F. Comprehensive analysis of EGFR T790M detection by ddPCR and ARMS-PCR and the effect of mutant abundance on the efficacy of osimertinib in NSCLC patients. *J*. 2019 Jul;11(7):3004-3014.
PubMed: PM31463130

17. Papadopoulou E, Tsoulos N, Tsantikidi K, et al. Clinical feasibility of NGS liquid biopsy analysis in NSCLC patients. *PLoS ONE*. 2019;14(12):e0226853.
PubMed: PM31860648

18. Soria-Comes T, Palomar-Abril V, Ureste MM, Guerola MT, Maiques ICM. Real-World Data of the Correlation between EGFR Determination by Liquid Biopsy in Non-squamous Non-small Cell Lung Cancer (NSCLC) and the EGFR Profile in Tumor Biopsy. *Pathol Oncol Res*. 2019 Mar 07;07:07.
PubMed: PM30847713

19. Zhang S, Chen Z, Huang C, et al. Ultrasensitive and quantitative detection of EGFR mutations in plasma samples from patients with non-small-cell lung cancer using a dual PNA clamping-mediated LNA-PNA PCR clamp. *Analyst*. 2019 Feb 25;144(5):1718-1724.
PubMed: PM30663747

20. Zhou J, Zhao C, Zhao J, et al. Re-biopsy and liquid biopsy for patients with non-small cell lung cancer after EGFR-tyrosine kinase inhibitor failure. *Thorac Cancer*. 2019 04;10(4):957-965.
PubMed: PM30887673

21. Arriola E, Paredes-Lario A, Garcia-Gomez R, et al. Comparison of plasma ctDNA and tissue/cytology-based techniques for the detection of EGFR mutation status in advanced NSCLC: Spanish data subset from ASSESS. *Clin Transl Oncol*. 2018 Oct;20(10):1261-1267.
PubMed: PM29623586

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PubMed: PM29922072

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28. Gu J, Zang W, Liu B, et al. Evaluation of digital PCR for detecting low-level EGFR mutations in advanced lung adenocarcinoma patients: a cross-platform comparison study. *Oncotarget*. 2017 Sep 15;8(40):67810-67820. PubMed: PM28978074

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PubMed: PM27448974

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PubMed: PM26206882

BRAF Biomarker Related Studies

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PubMed: PM31319569

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PubMed: PM29483107

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PubMed: PM29549923

44. Tang H, Kong Y, Si L, et al. Clinical significance of BRAF^{V600E} mutation in circulating tumor DNA in Chinese patients with melanoma. *Oncol*. 2018 Feb;15(2):1839-1844.
PubMed: PM29434880

45. Santiago-Walker A, Gagnon R, Mazumdar J, et al. Correlation of BRAF Mutation Status in Circulating-Free DNA and Tumor and Association with Clinical Outcome across Four BRAFi and MEKi Clinical Trials. *Clin Cancer Res*. 2016 Feb 01;22(3):567-574.
PubMed: PM26446943

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PubMed: PM26366702

BRAF Panel Related Studies

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PubMed: PM29707525

ROS1 Biomarker Related Studies

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PubMed: PM30664990

Studies Related to Multiple Biomarkers

49. Vitiello PP, De Falco V, Giunta EF, et al. Clinical Practice Use of Liquid Biopsy to Identify RAS/BRAF Mutations in Patients with Metastatic Colorectal Cancer (mCRC): A Single Institution Experience. *Cancers (Basel)*. 2019 Oct 08;11(10):08.
PubMed: PM31597339

50. Zugazagoitia J, Gomez-Rueda A, Jantus-Lewintre E, et al. Clinical utility of plasma-based digital next-generation sequencing in oncogene-driven non-small-cell lung cancer patients with tyrosine kinase inhibitor resistance. *Lung Cancer*. 2019 Aug;134:72-78.
PubMed: PM31319999

51. Thierry AR, El Messaoudi S, Mollevi C, et al. Clinical utility of circulating DNA analysis for rapid detection of actionable mutations to select metastatic colorectal patients for anti-EGFR treatment. *Ann Oncol*. 2017 Sep 01;28(9):2149-2159.
PubMed: PM28911069

Economic Evaluations

No literature identified.

Guidelines and Recommendations

No literature identified.

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Appendix — Further Information

Previous CADTH Reports

52. An Overview of Liquid Biopsy for Screening and Early Detection of Cancer. Ottawa: CADTH; 2019 Nov. (CADTH Issues in Emerging Health Technologies; Issue 179). https://www.cadth.ca/sites/default/files/hs-eh/eh0077-liquid-biopsy-for-early-detection-of-cancer.pdf (accessed 2020 Jan 10).

Additional References

Urinary ctDNA Cost Analysis

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