Real World Use of Circulating Tumor DNA (ctDNA) in Colorectal Cancer (CRC): A Targeted Literature Review (TLR)

Jones, Gieira, PhD, MSc[2]; Bagga, Shalini, PhD, MA[1]; Sood, Pallavi, PhD, MS[1]; Hariprasad, Esam, M.Pharma[1]; Mangla, Bhawna, M.Pharma[1]; Soni, Prashant, M.Pharma[1]; Sharma, Nidhi, M.Pharma[1]; Jain, Aastha, MA[1]; Goswami, Aanchal, MA[1]; Singh, Prashant, MSc[1]; Kumar, Sachin, M.Pharma[1]; Kothari, Smita, PhD[2]

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BACKGROUND

- According to International Agency for Research on Cancer, colorectal cancer (CRC) is the third most common cancer worldwide.[1]
- Almost 2 million new CRC cases were diagnosed in 2020 with global new cases expected to reach 3.2 million (an increase of 63%) per year and 1.6 million deaths per year (an increase by 73%) by 2040.[1,2]
- Circulating tumor DNA (ctDNA) is gaining attention as a bloos-based biomarker with the potential determine tumor-specific genomic profile, detect resistance (i.e., emergence of genetic alterations associated with drug resistance), and detect minimal residual disease (i.e., early diagnosis of relapse) to make informed therapeutic decisions.[2,3]
- Even though ctDNA represents a novel biomarker with clinical utility in different stages of cancers[3], it is unclear how ctDNA testing is being utilized in patients with CRC.

OBJECTIVES

- The aim of this targeted literature review is to characterize the uptake and use of ctDNA testing in real-world (RW) treatment of CRC.

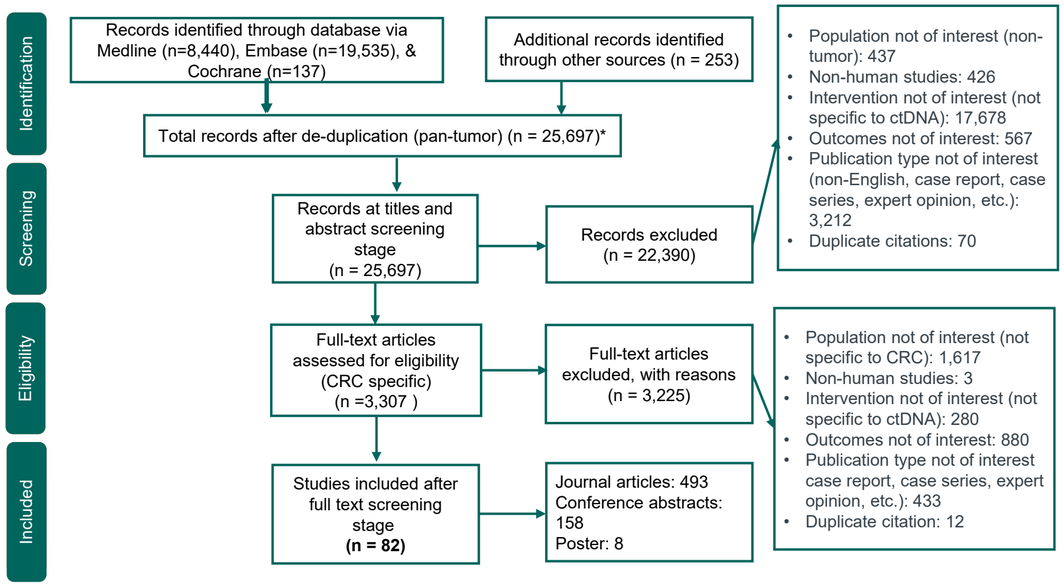
METHODS

- Targeted literature review was performed using Cochrane's Rapid Review Methodology.[4]
- Embase, Medline and Cochrane Database of Systematic Reviews were searched to identify relevant literature
- Search restricted to English-language publications, no time or geographic limits were imposed.
- Included studies focused on RW studies on adult CRC patients (>18 years) with **outcomes focusing on use and utilization of ctDNA for 2 aspects of interest: Molecular Profiling and Molecular Residual Disease.**
- No restriction on intervention or comparator.

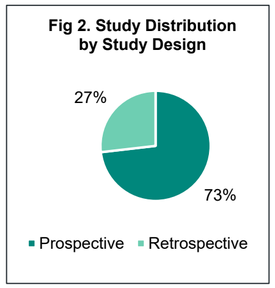
STUDY IDENTIFICATION AND CHARACTERISTCS

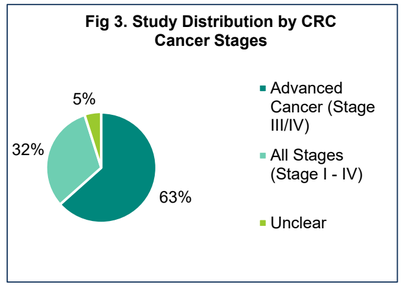
- 82 relevant studies included for this TLR.

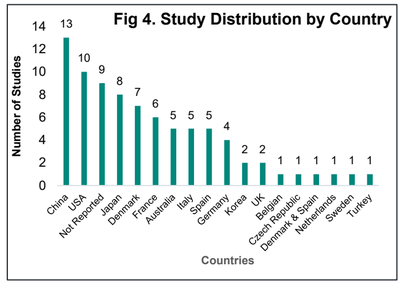
Fig 1. Flow Diagram for Identification of studies per **Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines**



**This number represents a larger pan-tumor project. After second step screening, only CRC studies were included.*

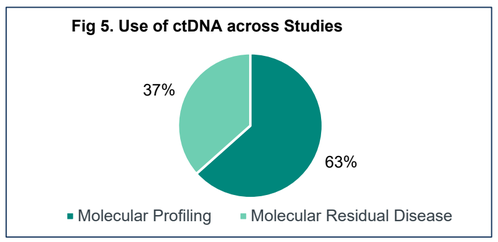


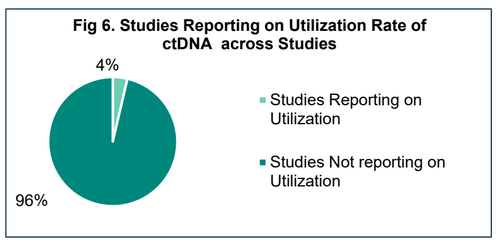




RESULTS: USE AND UTILIZATION OF ctDNA

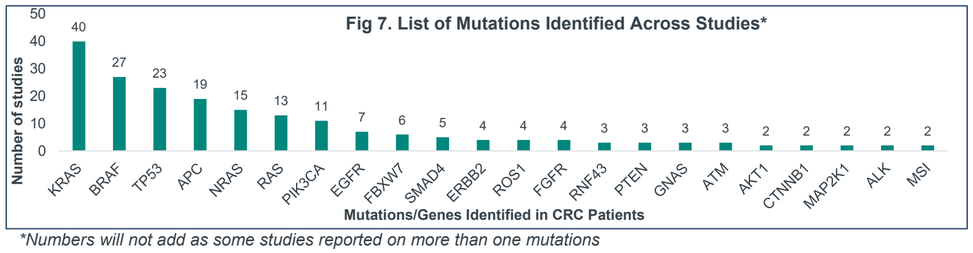
- Two studies reported true utilizations using data from- a RW claims database (Foundation Medicine Flatiron clinical-genomics database) and routine clinical practice respectively.[5,6]
- One study reported utilization using GuardantINFORM clinic-genomic database.[7]





RESULTS: MOLECULAR PROFILING

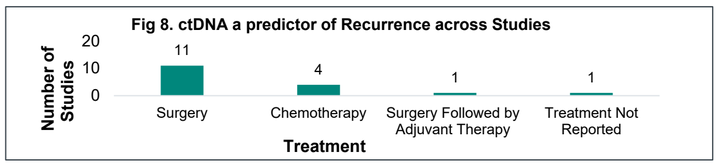
- Patients with KRAS, BRAF, RAS mutations detected in plasma presented with lower overall and progression-free survival.
- Molecular profiling studies demonstrated that mutations in CRC such as KRAS, NRAS, EGFR, RAS, BRAF, identified via ctDNA testing can guide treatment decisions.
- The concordance between tumor tissue mutation load and tumor plasma mutation load suggests that ctDNA can be used as an alternate to tissue biopsy.



**Numbers will not add as some studies reported on more than one mutations*

RESULTS: MOLECULAR RESIDUAL DISEASE

- 56% (17 out of 30) studies showed ctDNA to be associated with lower recurrence risk as a predictor of recurrence post treatment (Fig 8.)
- ctDNA positivity post treatment is strongly associated with detection of MRD, and early detection of relapse irrespective of treatment type.
- A strong association between ctDNA positivity and recurrence-free survival (RFS), and overall survival (OS) exists in patients with CRC irrespective of tumor stage, study size, tumor markers, detection methods.



CONCLUSION

- ctDNA testing is rapidly emerging as a useful tool for monitoring progressive genomic alterations and detecting residual disease post treatment.[8]
- Literature supports the concordance between tumor tissue mutation load and tumor plasma mutation load suggesting ctDNA could be a suitable alternate to tissue biopsy.[9,10,11]
- ctDNA as a molecular profiling tool can be extremely useful in therapeutic decision-making process
- ctDNA-based screening of patients with a higher risk of relapse may create opportunities for therapeutic intervention before the development of clinical metastasis.[8]
- Results suggest that positive MRD status is a promising predictor of early relapse detection of patients at high risk of recurrence.[12, 13, 14, 15, 17]
- There are gaps such as limited literature on utilization of ctDNA in RW that need to be addressed to determine true effectiveness of ctDNA testing in patients with CRC.

DISCLOSURES

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Full Sponsorship: This study was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

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