Final Topic Refinement Document

Role of Liquid Biopsy in Detection and Management of Cancer in the Medicare Population

ID: MYOE58

Agency for Healthcare Research and Quality

Technology Assessment Program

Mayo Clinic Evidence-based Practice Center

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Key Questions (KQ)

KQ 1: In adults with increased risk for lung, prostate, breast, ovarian, or colorectal cancer (e.g., BRCA carrier at increased risk for ovarian cancer), can a blood based liquid biopsy (defined for this project as circulating tumor cells [CTCs] and circulating tumor DNA [ctDNA]) be used as a targeted screening test?

KQ1a: What are the pre-analytic factors, analytic validity, and clinical validity of a blood based liquid biopsy?

KQ1b: What is the clinical utility of a blood based liquid biopsy?

KQ 2: In adults suspected to have lung, prostate, ovarian, or colorectal cancer (due to symptoms or signs), can a blood based liquid biopsy (defined for this project as CTCs and ctDNA) be used to establish a diagnosis of lung, prostate, breast, ovarian, or colorectal cancer?

KQ2a: What are the pre-analytic factors, analytic validity and clinical validity of a blood based liquid biopsy?

KQ2b: What is the clinical utility of a blood based liquid biopsy?

KQ 3: In adults with an established diagnosis of lung, prostate, breast, ovarian, or colorectal cancer, can a blood based liquid biopsy (defined for this project as CTCs and ctDNA) direct therapeutic decisions?

KQ3a: What are the pre-analytic factors, analytic validity and clinical validity of a blood based liquid biopsy?

KQ3b: What is the clinical utility of a blood based liquid biopsy?

Draft Analytic Framework

Figure 1 A. Liquid biopsy used in a targeted screening paradigm

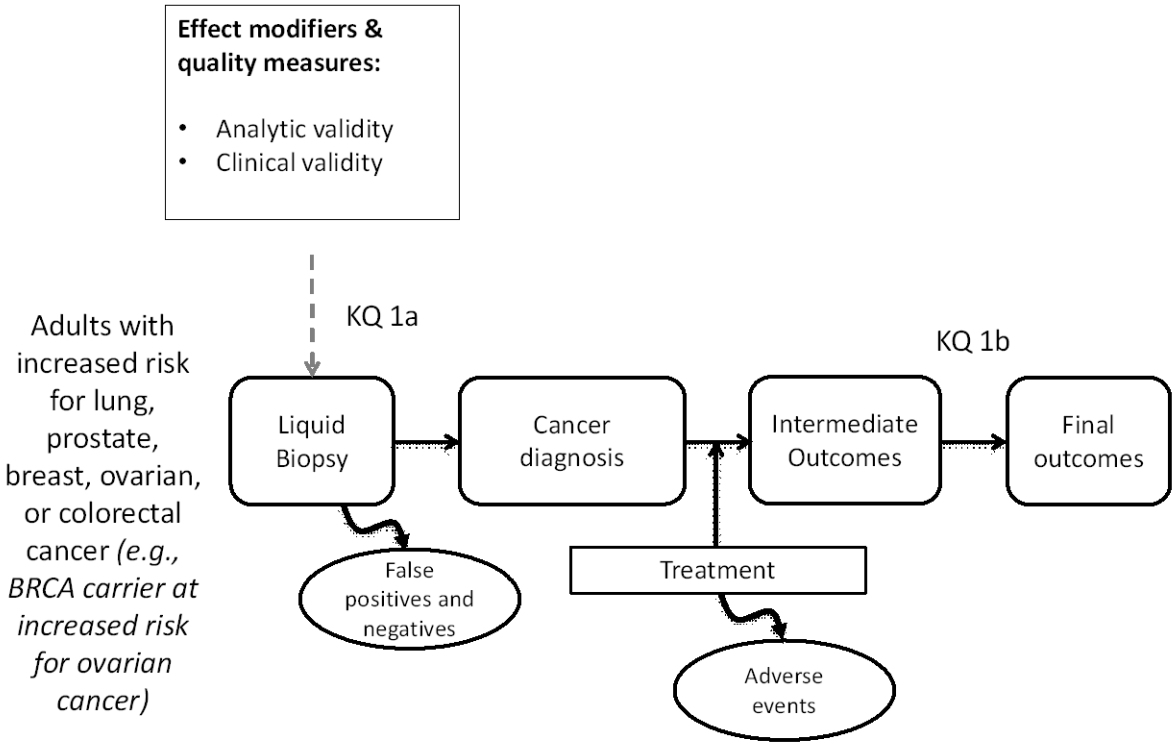
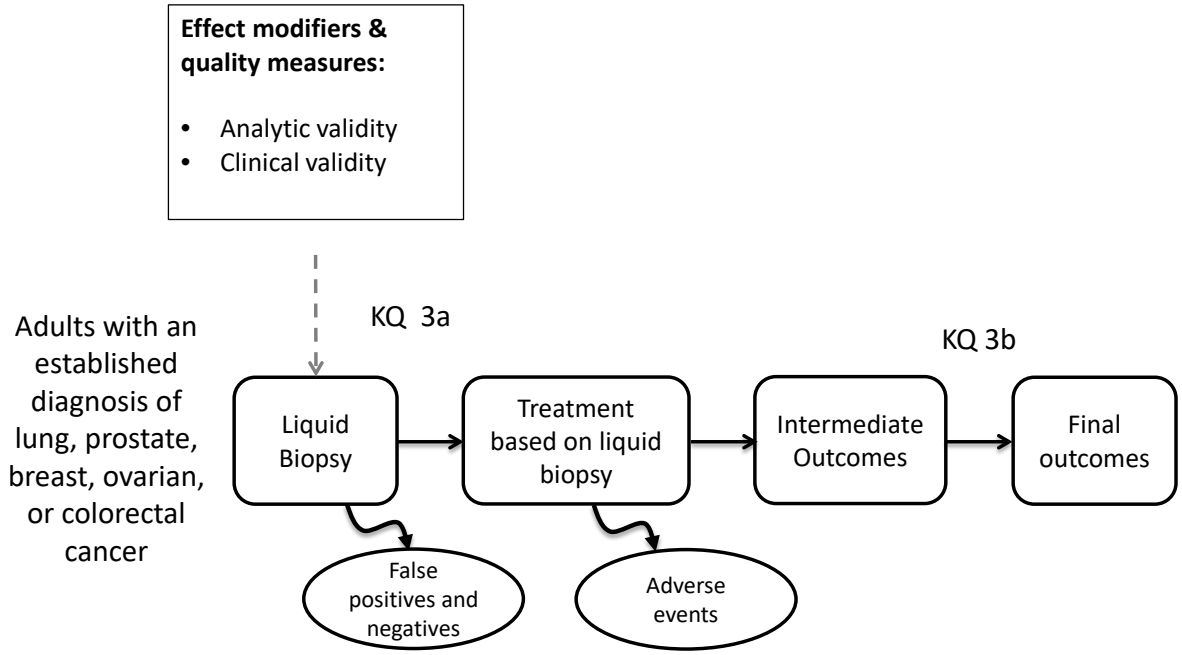


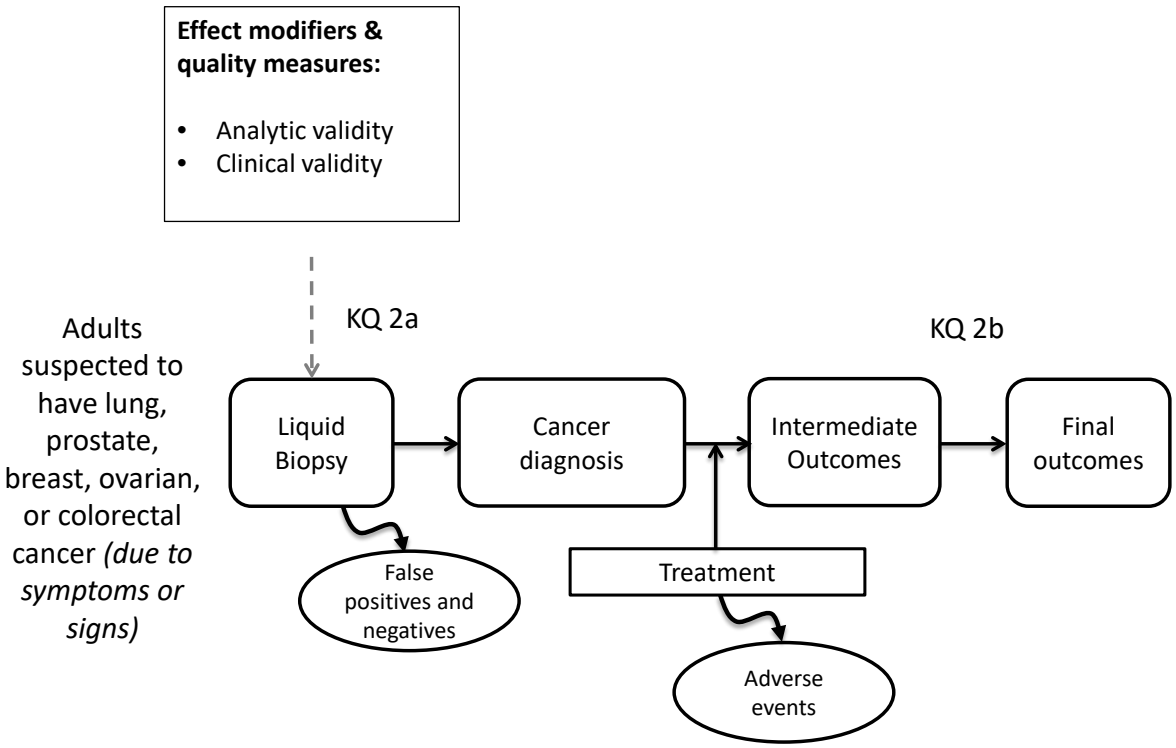
Figure 1 C. Liquid biopsy used in a therapeutic paradigm



Background

Recent technologic advances have allowed for the isolation and analysis of CTCs,

Figure 1 B. Liquid biopsy used in a diagnosis paradigm



ctDNA, and extracellular microvesicles, making the promise of a liquid biopsy possible. A liquid biopsy is defined as the analysis of tumor related material in a sample obtained from the peripheral blood. This material includes intact cells, and nucleic acids (DNA or RNA). Compared to a tissue biopsy, which requires a surgical or image guided procedure to obtain a tissue sample, blood collection by venipuncture is a much less invasive diagnostic approach. Liquid biopsy has been studied in numerous solid tumor types and in hematologic malignancies. However, the majority of the literature in the last decade has been focused on lung cancer, prostate cancer, breast cancer, ovarian cancer, and colorectal cancer. The scope of this topic refinement document focuses on circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) and excludes other biomarkers and methylation based tests.

Regulatory considerations:

Liquid biopsies that are manufactured and performed within a single laboratory [a laboratory with a single certificate issued by the Clinical Laboratory Improvement Amendments (CLIA) program] are considered laboratory developed tests (LDTs). These liquid biopsies are not currently regulated by U.S. Food and Drug Administration (FDA). They are overseen by the CLIA program to ensure analytically accurate and reliable test results. The position of the FDA may change in the future as the FDA has issued a discussion paper on LDTs in 2017 but without an enforceable action.[1] The CLIA final rules specify that the actual performance characteristics of LDTs must be comparable to their claimed specifications in the following areas: accuracy, precision, reportable range of results, reference intervals (normal ranges), analytical sensitivity (detection limit), analytical specificity (interferences/cross reactivity) and any other relevant performance characteristics for the particular test/testing system.

Clinical applications and dilemmas:

Potential clinical scenarios in which a blood based liquid biopsy can be used include screening in asymptomatic individuals at increased risk for cancer, a diagnostic tool in patients suspected to have cancer (such as those with symptoms, thus reducing the need for an invasive tissue biopsy), or as a therapy-guiding tool in patients with established cancer diagnosis (to aid in treatment decisions such as choosing the initial treatment, determining response to a treatment or modifying a treatment).

In terms of screening (identifying disease in an early stage aiming at reducing cancer mortality and morbidity), one important challenge is that screening requires studies with a very large sample size because cancer incidence in asymptomatic individuals is generally low; therefore, sensitivity and specificity cannot be reliably estimated.[2] In addition, because of statutory limitations on screening/prevention services from CMS perspective,[3-6] targeted disease screening would involve a smaller population with a much higher risk, e.g., ovarian cancer in BRCA carriers. In a diagnosis paradigm, a traditional biopsy will likely be preferred in many situations, particularly because patients may anyway require an excision of a mass and a surgical intervention. It remains unclear whether a liquid biopsy can reduce downstream testing, costs and improve hard endpoints, such as survival, when used as a tool to establish diagnosis or guide treatment decisions.

Validity of a medical test:

For a medical test such as the liquid biopsy to be used in practice, several conditions are required.[7] Pre-analytic factors should be evaluated (i.e., the test needs to conform to technical specifications that relate to the collection, handling and storage of the specimen). The test needs to have sufficient analytic validity (i.e., the test needs to measure the substance of interest in an accurate manner concordant with a gold or reference standard), clinical validity (i.e., the test needs to have diagnostic accuracy in classifying the target population) and clinical utility (i.e., the test needs to demonstrate improvement in patients' management and outcomes).

Therefore, a systematic review of the utility of liquid biopsy should collect data on these domains of validity and consider them as markers of methodological quality and possible covariates that can explain heterogeneity.

Current State of the Evidence

We searched six databases (Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus) from January 1st, 2000 to October 3rd, 2019. We searched comparative studies of liquid biopsy for any type of cancer. We limited our search to randomized controlled trials (RCTs), observational studies, systematic reviews/meta-analyses (SR/MA), and clinical guidelines. No language restriction was used. A total of 8,998 citations were identified, including 8,881 RCTs and observational studies and 117 systematic reviews/guidelines. Then we conduct manual screening of RCT, observational studies, SR/MA, and guidelines. 216 studies were deemed relevant, including 3 RCTs, 198 observational studies, and 12 SR/MA. We present the distribution of studies by cancer, objective (targeted screening in individuals with increased cancer risk/diagnosis and treatment selection/monitoring), and study design in Table 1. In addition, we also identified 128 ongoing trials from ClinicalTrials.gov; which suggests high interest from researchers and manufacturers and indicate that a future systematic review will likely identify more studies than what is included in this topic refinement document.

Table 1: Literature Search and Impact of Scope Decisions on Size of Potential Evidence

Search Description	Objective	Subcategories	Citations
Overall	Targeted screening in individuals with increased cancer risk/diagnosis	TOTAL	160
		RCTs	0
		Observational studies	148
		SR/MA	12
		Guideline	0
	Treatment selection/monitoring	TOTAL	56
		RCT	3
		Observational studies	50
		SR/MA	3
		Guideline	0
Breast Cancer	Targeted screening in individuals with	TOTAL	41

Table 1: Literature Search and Impact of Scope Decisions on Size of Potential Evidence			
Search Description	**Objective**	**Subcategories**	**Citations**
	increased cancer risk/diagnosis	RCT	0
		Observational studies	39
		SR/MA	2
		Guideline	0
	Treatment selection/monitoring	TOTAL	56
		RCT	3
		Observational studies	50
		SR/MA	3
		Guideline	0
Colorectal Cancer	Targeted screening in individuals with increased cancer risk/diagnosis	TOTAL	15
		RCT	0
		Observational studies	14
		SR/MA	1
		Guideline	0
	Treatment selection/monitoring	TOTAL	0
		RCT	0
		Observational studies	0
		SR/MA	0
		Guideline	0
Lung Cancer	Targeted screening in individuals with increased cancer risk/diagnosis	TOTAL	58
		RCT	0
		Observational studies	52
		SR/MA	6
		Guideline	0
	Treatment selection/monitoring	TOTAL	0
		RCT	0
		Observational studies	0
		SR/MA	0
		Guideline	0
Ovarian Cancer	Targeted screening in individuals with increased cancer risk/diagnosis	TOTAL	26
		RCT	0
		Observational studies	24
		SR/MA	2
		Guideline	0
	Treatment selection/monitoring	TOTAL	0
		RCT	0
		Observational studies	0
		SR/MA	0
		Guideline	0
Prostate Cancer	Targeted screening in individuals with increased cancer risk/diagnosis	TOTAL	20
		RCT	0
		Observational studies	19

Table 1: Literature Search and Impact of Scope Decisions on Size of Potential Evidence			
Search Description	**Objective**	**Subcategories**	**Citations**
		SR/MA	1
		Guideline	0
	Treatment selection/monitoring	TOTAL	0
		RCT	0
		Observational studies	0
		SR/MA	0
		Guideline	0

*Ongoing trials identified from ClinicalTrials.gov were not included in this table.

MA = meta-analysis; RCT = randomized controlled trial; SR = systematic review

Draft Population, interventions, comparisons, outcomes, timings and settings (PICOTS)

Population(s)

- Adult patients (18 years and older)
- Patients at increased risk (KQ1), suspected to have (KQ2), or have an established diagnosis (KQ3), of:
    - lung cancer
    - prostate cancer
    - breast cancer
    - ovarian cancer
    - colorectal cancer

Intervention (test)

- Blood based liquid biopsy based on circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA)

Comparators

- Targeted screening, diagnosis or management without liquid biopsy

Outcomes

- Intermediate outcomes
    - Sensitivity, specificity, inter- and intra-laboratory reproducibility (domains of analytic and clinical validity)
    - Downstream testing and procedures
    - Cancer stage at diagnosis
- Final outcomes
    - Overall survival, and harms

Timing

- Any duration of follow-up

Settings

- Any

Subgroup analyses/possible effect modifiers

- Designated as LDT vs. FDA approved test
- Patient characteristics that may interfere with test performance, such as autoimmune disorders

- Different assays
- Adequacy of pre-analytic factor
- Cancer stage
- For KQ3, treatment type (surgery vs. radiotherapy vs. chemotherapy)

Study design

- Randomized controlled trial
- Longitudinal comparative observational studies

Definition of Terms in the context of this topic refinement document

Term	Definition
Liquid biopsy	A minimally invasive test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for fragments of tumor-derived DNA that are in the blood.[8]
Pre-analytical factors	Issues regarding collection, handling, transport, processing, and storage of a specimen that may affect the subsequent analysis.[8]
Analytic validity	Ability of an assay to detect and measure, with statistical significance, the presence of a substance of interest accurately, reproducibly, and reliably.[8]
Clinical validity	Ability of an assay to divide, with statistical significance, one population into two or more groups on the basis of outcomes.[8]
Clinical utility	Ability to demonstrate, with statistical significance, improvement in the diagnosis, treatment, management, or prevention of cancer, with the use of the assay compared with not using the assay.[8]

DNA = deoxyribonucleic acid

Abbreviation list

Acronym	Definition
AHRQ	Agency for Healthcare Research and Quality
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centers for Medicare & Medicaid Services
CTC	Circulating tumor cell
ctDNA	Circulating tumor DNA
DNA	Deoxyribonucleic acid
EGFR	Epidermal growth factor receptor
EPC	Evidence-based practice center
FDA	Food and Drug Administration
KQ	Key question
LDT	Laboratory developed tests
PICOTS	Population, interventions, comparisons, outcomes, timings and settings
PMA	Premarket approval

Acronym	Definition
RCT	Randomized controlled trial
RNA	Ribonucleic acid
SR	Systematic review

Role of the Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism. Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. AHRQ and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

Summary of disposition of public comments to Draft Key Questions and supporting material

- The document in general has received a large number of lengthy and detailed comments; which suggests great interest in the topic.
- A large number of comments were from industry (manufacturers of particular types of liquid biopsy tests). These comments have been carefully considered in the context of potential conflicts of interest. CMS has provided additional comments, which are included in Appendix A.
- Several comments suggested excluding screening from the proposed systematic review citing lack of evidence and the need for large studies to demonstrate an effect. However, screening was of interest to the patient representative and other stakeholders. New literature about screening also appears to be emerging. Therefore, screening will continue to be one of the paradigms of using liquid biopsy to be evaluated in the proposed systematic review.
- Several comments suggested excluding diagnosis from the proposed systematic review citing lack of evidence and the fact that tissue biopsy will always be needed for starting definitive cancer therapies. However, diagnosis was of interest to some of the stakeholders that we have interviewed. Therefore, screening will continue to be one of the paradigms of using liquid biopsy to be evaluated in the proposed systematic review.
- Some comments suggested expanding the number of malignancies studied beyond the proposed 5 (lung, prostate, breast, ovarian and colorectal cancer). From feasibility standpoint, this may make the scope of the review challenging. In addition,

the interviewed key Informants have advised to focus on these 5 tumors because they are the most common and also because the majority of the available literature will be about these 5 types.

- Some liquid biopsy manufacturers recommended expanding the type of assay, for example to ones studying exosomes. Key informant interviews have suggested that these other types are experimental and advised to evaluate assays that measure CTCs and ctDNA.
- Some comments addressed various issues about pre-analytic factors, analytic and clinical validity, and clinical utility. In general, these domains remain critical to evaluate in the proposed systematic review regardless of paradigm (i.e., screening, diagnosis, guiding-therapeutic decisions).

Key Question changes

Public comments were discussed with Centers for Medicare & Medicaid Services (CMS) and Agency for Healthcare Research and Quality (AHRQ) in June 2020 as part of topic refinement. Based on the discussion, these changes were made:

KQ 1: we have focused the question to include patients with increased risk for lung, prostate, breast, ovarian, or colorectal cancer, and added the BRCA carrier as an example to emphasize that this question focuses on targeted screening of high risk individuals.

KQ 2: we clarified that patients suspected to have lung, prostate, breast, ovarian, or colorectal cancer, are patients with symptoms or signs suggestive of cancer who need a diagnostic test (as opposed to a screening paradigm).

All KQs: We added new subgroup analyses by cancer stage and treatment type (surgery vs. chemotherapy vs. radiotherapy). We emphasized the importance of hard endpoints, particularly, overall survival. We used a broad term for the comparators, which is" screening/diagnosis/management without liquid biopsy", in order to include tissue biopsy and other tests, and to include any study settings. We added cancer stage at diagnosis and downstream testing and procedures as intermediate outcomes.

References

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Appendix A: Sponsoring Partner Comments

The EPC received the following comments from CMS:

- CMS notes the relationship between ILLUMINA and GRAIL who each made many comments.
- CMS notes the 9/9/2020 initial public offering by GRAIL and their screening test using methylation.
- CMS notes the role of a Mayo physician as a key informant for this project and as an investigator for a key GRAIL study—a conflict not known by CMS.
- CMS notes the 2019 departure of Josh Ofman (gastroenterologist) from Amgen to GRAIL and ILLUMINA's panel linkage to Amgen's drug panitumumab.
- CMS notes the many comments trying to get screening and diagnosis eliminated from the project and how those commenters wanted assessment of how the test could be used to "help management".
  - No mention was made of the specific pairing with certain drugs.
  - No mention was made of issues (utility) when there was more than one mutation at a single time or when there were serial mutations after evolutionary pressure.

https://www.genomeweb.com/molecular-diagnostics/illumina-receives-fda-approval-companion-dx-run-miseqdx#.X4zFRVhlLIU

Illumina has received US Food and Drug Administration approval for a companion diagnostic test, which it has been developing with Amgen, to run on its MiSeqDx system, the company said after the close of the market on Thursday.

The Extended RAS Panel analyzes 56 variants in the KRAS and NRAS genes to determine whether patients will benefit from Amgen's Vectibix (panitumumab), which is approved for patients with metastatic colorectal cancer who have wild-type KRAS and NRAS genes. Illumina will begin shipping the panel in the third quarter.

Last December the agency approved Foundation Medicine's FoundationFocus CDxBRCA test to identify advanced ovarian cancer patients who have mutations in their BRCA1 and BRCA2 genes and are therefore more likely to benefit from Clovis Oncology's PARP inhibitor Rubraca (rucaparib).

And last week the FDA approved a test developed by Thermo Fisher Scientific in collaboration with AstraZeneca, Pfizer, and Novartis, to identify non-small cell lung cancer patients who are best responders to those pharmaceutical companies' respective drugs.

'The largest application we can imagine': Illumina and Grail CEOs defend their deal to investors ***By*** *Matthew Herper @matthewherper September 25, 2020*

Shares of Illumina, the leader in DNA sequencing, have dropped 13% since news leaked last week that the company would be buying Grail, a startup developing a blood test to detect cancer. Obviously, not every investor loves the $8 billion deal.

But in an interview with STAT, the CEOs of the two firms — Illumina's Francis deSouza and Grail's Hans Bishop — said it would take time for investors to understand the advantages of combining the two firms. They argue that is particularly true in regard to the potential market for Grail's two tests: Galleri, which will aim to detect cancer early in apparently healthy people, and a second, unnamed test, which is being designed to test for potential cases of cancer in patients who have symptoms of the disease.

Filed 9/9/2020
https://www.statnews.com/2020/09/25/illumina-grail-investors-deal/
Grail, a spin out of genome sequencing firm Illumina, filed a preliminary prospectus for a $100 million initial public offering (IPO) last week with the U.S. Securities and Exchange Commission (SEC). This move precedes the company's anticipated 2021 launch of a multi-cancer liquid biopsy screening test for use in asymptomatic individuals over the age of 50.

Grail expects to launch their liquid biopsy product Galleri as a lab-developed test next year. Galleri relies on a targeted methylation sequencing panel to identify more than 50 types of cancer across different stages of disease. Additionally, the blood-based test is designed to help clinicians identify a cancer's tissue of origin. The company is planning for commercialization of their product, and a premarket approval application for a next-generation version of the test has been scheduled for submission in 2023.