Multi-Cancer Early Detection tests –
Will they become part of regular clinical care?

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Summary

The idea of a single blood-test to detect many cancers is attractive, but is it practical? Can an MCED enhance, or even replace, current screening tests?

This paper delves into these questions by reviewing the effectiveness of current cancer screening methods and identifying areas with the most unmet need. We examine results of Grail's PATHFINDER2 study on Galleri®, one of the first tools designed to detect many cancers in a single test. However, the test's adoption will depend on cost-effectiveness, which considers price, cancer detection rate, and associated subsequent diagnostic and clinical care costs.

As Grail and others pursue the pan-cancer approach in ever larger cohorts, we ask ourselves: Should we be screening everyone for every cancer, or is it better to focus on the diseases (or individuals) most likely to succumb to disease?

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The state of multi-cancer early detection (MCED) tests today

In October of this past year, the preliminary results of the first prospective study on a blood test intended for cancer detection were published in the Lancet.[1] This is the first, and smallest, in a series of studies sponsored by Grail on the viability and clinical benefit of early-cancer detection by their multi-cancer early detection (MCED) test, Galleri® (Table 1).[2] Larger studies aim to determine if use of the test can alter the rate of early-stage disease detection, cancer mortality, morbidity and associated healthcare spending.

More recently, the Molecular and Clinical Genetics Advisory Committee at the FDA held a day- long session to discuss clinical trial designs, importance of tissue-of-origin data, and benefits and risks for use in real-world clinical settings.[3] As public and private interest in these non-invasive tools grows, we thought it would be useful to explore both the state of cancer-screening and cancer treatment outcomes today, to understand where a "liquid-biopsy" screening could be a useful addition to preventative care.

Why screen for cancer at all?

It may seem obvious, but it bears emphasis: the reason we screen for cancers is to reduce cancer mortality and morbidity. That means we don't just want to find the most common cancers, rather the most common and lethal - which is where the most impact can be had (in terms of lives saved or improved). As can be seen in Figure 1,[4] while non-melanoma skin cancer is far-and-away the most common (10x ~higher incidence than the next most frequent cancer, breast cancer), it is rarely lethal. In fact, if we prioritize by annual deaths, a completely new priority emerges, and the top 3 cancers (lung, colorectal, pancreatic) lead to >37% of all deaths. Of course, lethality is a mix of aggressiveness and stage of disease – part of the reason lung and pancreatic cancers both float to the top on annual deaths is due to their typically late-stage diagnosis.

We propose a framework that characterizes not just the number of potential diagnoses, but also the relative unmet need. As shown in Figure 2, comparing lethality of cancer by stage (odds ratio of 5-year survival for local vs. regional diagnoses) against the share of cases diagnosed in early stage, a clear delineation occurs. Diseases in the right half

Table 1: Disclosed trials on Grail's multi-cancer early-detection (MCED) test, also known as Galleri®

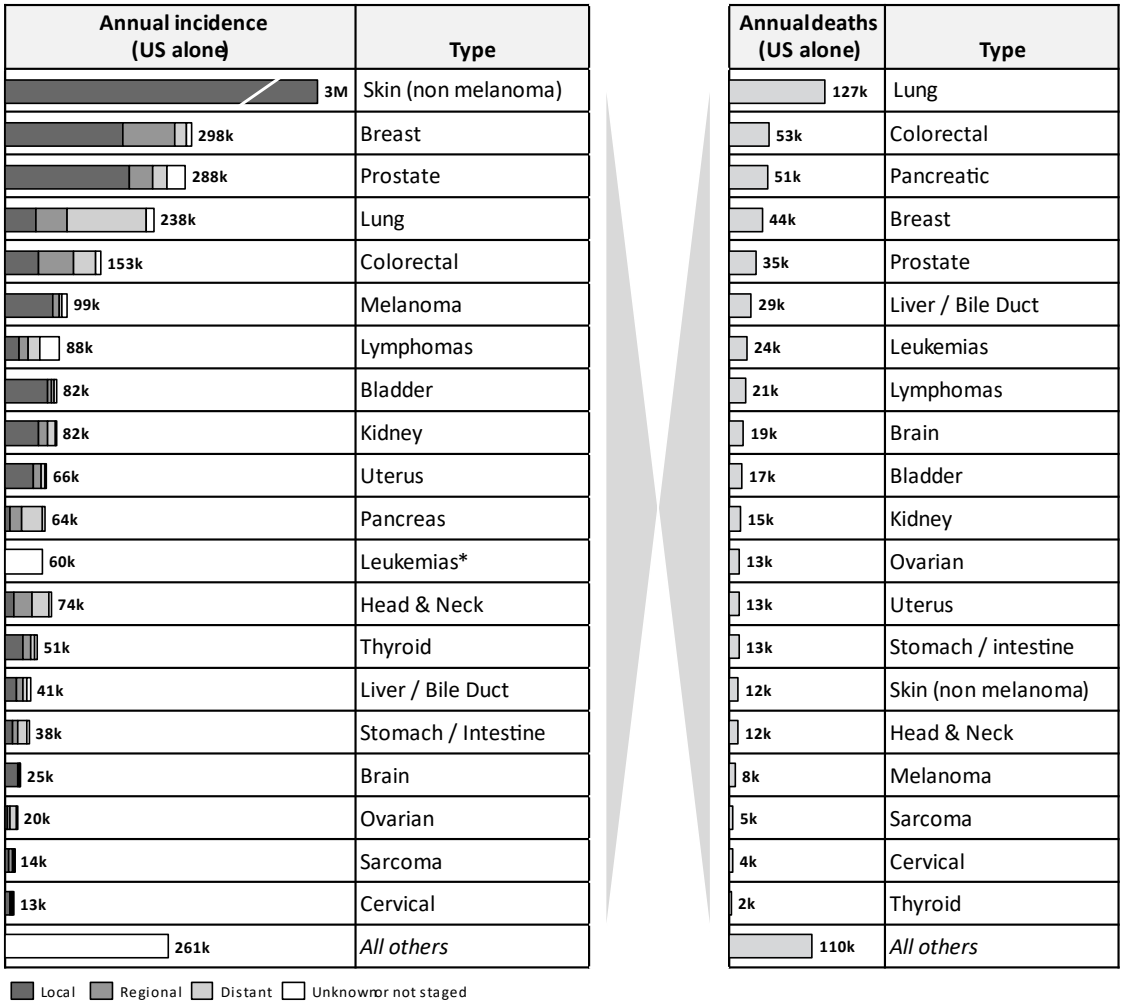
Study	Type	Cohort size	I/E criteria	Control arm	Outcomes measured	First readout	Final readout
PATHFINDER2	Prospective	6,600	• ≥50 years old • Cancer-free prior 3 yrs	None	• MCED test result (single test) • Timeline to diagnosis (12mo)	Late 2023	Late 2026
REFLECTION	Observational	17,000	• ≥22 years old	None	• MCED test result (single test) • PRO[b] over 12mo • HCRU[b] over 12mo	Early 2025	Late 2026
NHS-Galleri	Prospective	140,000	• 50 – 77 years old • Cancer-free prior 3 yrs	Randomized 1:1 to SOC screening	• MCED result (annual for 3-yrs) • Late-stage diagnoses (at Y1) • HCRU[1] over 3-years of testing • Cancer-mortality rates (Y4, Y7 and Y10) for 12 specified cancers[3]	Early 2025	Late 2028
REACH	Prospective	50,000	• Medicare enrollees (i.e., ≥65 years old)	Synthetic from RW data (EMRs)	Details remain in development • MCED result • Late-stage cancer diagnoses • HCRU (undiscl timeline)	Early 2025	Unknown

(e.g., pancreatic, liver, stomach, lung) have the worst survival rates, while those on the bottom-half (e.g., colorectal, lung, ovarian, pancreatic) are most often diagnosed in later-stages. The greatest changes are likely to be found via increased early-stage detection for disease in the lower-right quadrant (e.g., pancreatic, liver, stomach and lung), with diminishing returns moving toward the top-left quadrant.

A couple of points regarding this framework and the placement of various diseases within it:

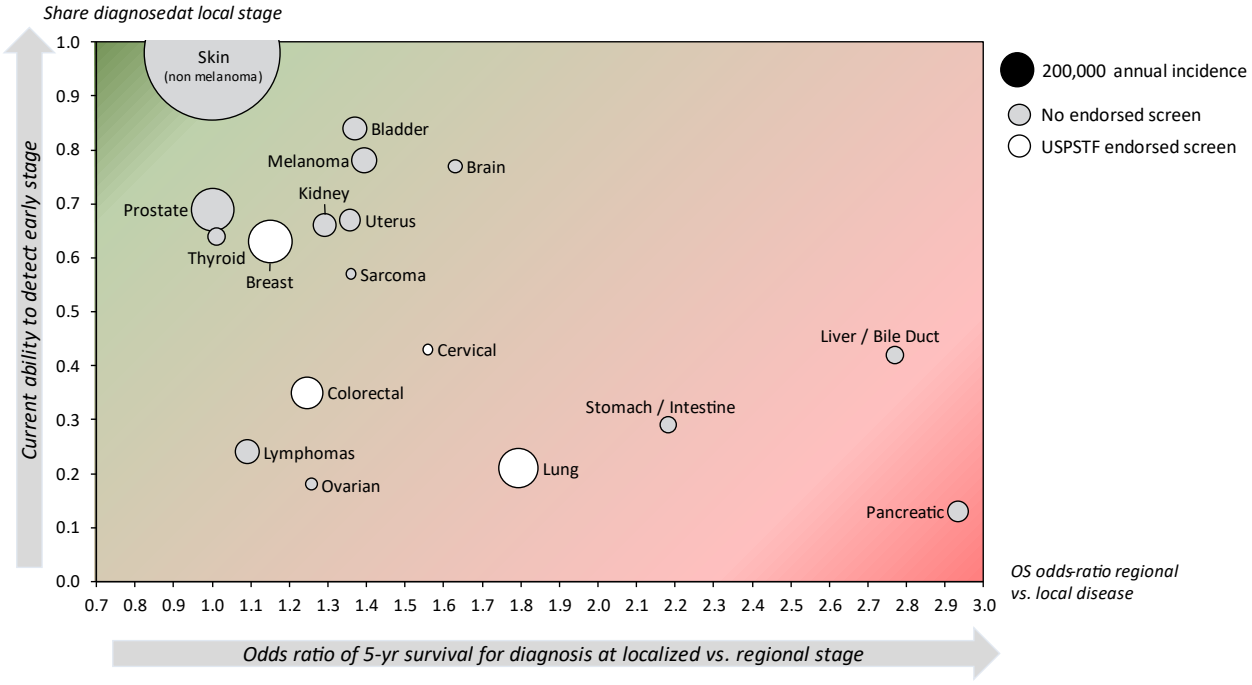
- Hematologic malignancies are not staged in the same way as solid tumors. We used regional involvement as a surrogate for lymphomas, but other blood-cancers (including leukemias) could not be categorized by our approach.
- Impact of existing screening programs on early-stage detection is captured by this framework; y-axis placement (share diagnosed at local stage) reflects both tests innate sensitivity and screening-adherence.
- *Carcinoma in situ* is a substantial share of "local" breast and bladder cancers (18-25%and 50%, respectively). The value of detection and treatment for these "precancers" is somewhat controversial, particularly in the case of breast (i.e., increased detection and treatment of DCIS in breast has not affected breast cancer survival rates).[5]

Figure 1: Cancer statistics across disease types



Source: Recon analysis of SEERdata. * Note that Leukemias (and many other heme cancers) are not staged as solid tumor cancers.

Figure 2: Relative unmet need for early-stage cancer detection



In some cancers, screening programs have already improved diagnosis and outcomes

For cervical, breast, lung and colorectal cancers, the rate of early-stage detection has been improved in recent decades through alternative screening tests, which have been studied extensively.[6] As can be seen in Table 2, a range of cancer-screening tests are available. However, not all cancer-screening tests are endorsed by the United States Preventive Services Task Force (USPSTF),[7] as not all are believed to offer sufficient clinical benefit. The underlying driver of low clinical value can be due to myriad factors, including:

- Inadequate sensitivity - particularly when an alternative, more sensitive test is available (e.g., chest x-ray vs. LDCT for lung cancer[8])
- High false-positive rates where the subsequent diagnostic confirmation is highly invasive and the cancer rare (e.g., CA125 for ovarian, wherein biopsies used for diagnosis can only be obtained surgically[9])
- Detecting indolent disease, which leads to treatment of cancers that would otherwise not cause mortality (e.g., prostate,[10] thyroid[11])

Some of these tests also detect precancerous lesions (e.g., colonoscopy, Pap smear) which can be treated – thereby reducing the incidence for those cancers. However, many also suffer from substantive false-positive rates and adherence is often low. Any test that seeks to replace endorsed programs must improve overall cancer outcomes and spending – and it is important to consider the greater risk of false-positives in low-incidence cancers. As highlighted in Figure 3, (borrowed from Brownstein *et al*[20]), the effect means that the cost of follow-up testing will be intensified for the least common cancers. Unless the cost of definitive diagnosis is marginal, this suggests stricter sensitivity/specificity criteria may be appropriate for the rarest diseases (e.g., ovarian, sarcoma).

Table 2: Alternative cancer-specific screening tests

Cancer Type	Screening test		USPSTF opinion		Screening program adherence
	Method	False-pos rate[i]	Endorsement	Justification	
Breast	Mammogram	4.9%[12]	Biannually (age 50-74)	General screening shown to reduce breast cancer deaths (42 fewer per 300,000 patient-years); however, data shows ~20% of mammogram-diagnosed breast cancers do not become life-threatening	30-76%[13]
	BRCA germ- line mutation	-	*Only if strong family history*	Rare mutation in general population (~0.2% prevalence), but up to 20% for those with strong family history (or certain ethnic groups); accounts for <10% of all breast cancer cases	-
	Ultrasound	16%[14]	No	Inconsistent characterization as BiRADs "dense"; data unclear on whether usage detects additional cancers (vs. mammography alone) or has affect on treatment decisions / cancer-mortality	-
	MRI	28%[15]			
Lung	LDCT	~7%[16]	Annually, for 20-pack-year	Screening reduces lung cancer mortality 16-20% (vs. no screening or chest-radiography alone) in former smokers; false-positives can be moderated by decision to "wait-n-monitor" before biopsy	<25%[5]
Colorectal	Colonoscopy	n/a[ii]	Every 10 years (age 45-74)	Screen detects cancerous ***& pre-cancerous*** lesions; latter can be removed during screening; clear mortality benefit (337LYG/1,000 screened) for low frequency; moderate SAE (25/10,000 procedure)	58% (*Overall: 67%*[17])
	Flexible sigmoidoscopy	n/a[ii]	Every 5 years (age 45-74)	Slightly lower benefit *vs* colonoscopy (286LYG/1,000 screened), with a lower risk of SAE (<4/10,000 procedures)	~1%
	Fecal occult blood test	<10%	Every 5 years (age 45-74)	Less sensitive than colonoscopy, but little/no SAE risk; improved patient comfort (facilitates adherence) with similar mortality impact for more frequent testing (298LYG/1,000 screened)	~7%
	Fecal DNA (*aka* Cologuard®)	~16%	No	~Equiv benefit as colonoscopy (333LYG/1,000 screened) if used ***annually*** (5-10x more frequent than above); at current pricing, test cost ~same as above procedures (so 5-10x spend for equal benefit)	-
	CT colonography	7-16%	No	High rate of "extracolonic findings" (*left*) lead to more imaging; ~equiv benefit as colonoscopy (317 LYG/1,000 screened) with similar risk of perforation and SAEs (0– 6 for every 10,000 procedures)	-
Cervical	Pap smear	~10%	Every 3 years (age 21-65)	Precursor HPV endemic; screen detects cancerous and pre-cancerous lesions, latter can be removed *via* minimally invasive, in-office procedure (prevents new cancers); ~70,000LYG/1,000 screened	80%[18]
Prostate	Prostate-specific antigen	5%	No	99% 10-year OS without treatment (99% if treated); for radiation treatment, 20% develop erectile dysfunction; for radical prostatectomy, 20% develop urinary incontinency, 65% erectile dysfunction	-
Thyroid	Ultrasound	17-46%[19]	No	97% 5-year OS without treatment (99% if treated); autopsies show >11% with papillary carcinoma	-
Ovarian	CA125 antigen (+/- ultrasound)	9-10%	No	High false-positive rate for a rare cancer (1/10,000); definitive diagnosis requires surgical excision of the organ (~15% surgical SAEs); studies showed no benefit to cancer-mortality of screening	-

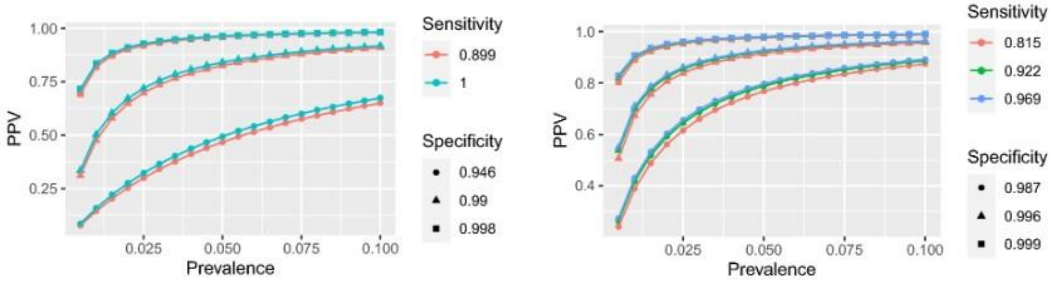
Notes: Unless otherwise referenced, all data comes from USPSTF Recommendation statements for screening for Breast, Lung, Colorectal, Cervical, Prostate, Thyroid and Ovarian cancer. (i) Average rate of screen-test positives that are subsequently determined to be benign/non-cancerous in definitive diagnostic test workup; effects over multiple screening events are typically ~additive, but share of false positives may be different at initial screening event compared to subsequent screens. (ii) Definitive diagnosis is made via pathology of any suspicious polyps or lesions detected, leaving only false-positives due to pathology errors.

Grail takes a "blue sky" approach - looking for all cancer-types

Galleri® works by identifying cell-free DNA fragments in blood with unusual methylations, which are indicative of carcinogenicity. Blood-borne DNA fragments can originate from any part of the body, and as a result, this test can detect >50 cancer-types.[21] The recent Lancet paper[1] study found, over all cancer types, Galleri® had low false-positivity rates (0.9%).[22] However, since the level of need varies by cancer (as well as the associated cost and risk of follow-up diagnostic tests), we believe it is crucial to understand performance (both sensitivity and specificity) on a disease-by-disease basis.

Looking into disease-by-disease results of PATHFINDER2 (Table 3), it quickly becomes clear that much larger cohorts will be needed to observe a substantial number of cancer cases in the general population.[23] However, these preliminary results suggest Galleri® is unlikely to replace existing tests

Figure 3: Effect of different sensitivity/specificity on positive predictive values at low prevalence



- more cancers were seen *via* standard clinical care and screening (i.e., suggesting a lower sensitivity than existing SOC tools). Even the share of early-stage diagnoses was no better from Galleri® than SOC. Until more definitive data is seen, it seems Galleri® is likely to be relegated to add-on to existing screening programs and SOC testing. Clearly, the tool can detect diseases which have no effective screening tools today, and even a modest sensitivity here could improve outcomes (e.g., pancreatic, liver and stomach cancer). However, adding this test to clinical practice does have risks: (1) a negative Galleri® test could be used to justify delayed (or non-adherence) screening *via* more sensitive tests for lung, colorectal or breast cancer, (2) increased general screening will lead to more diagnostic follow-up tests (many of which will turn out to have been false-positives; as discussed above, this will be most common in the rarer cancers).

Will it make sense to add Galleri® (or any MCED) as a screening tool?

Adding a new screening tool comes down to cost effectiveness, which relies heavily on **both** the test cost and impact on cost/outcomes of subsequent care. This analysis can only be achieved by tracking the total healthcare resource utilization (HCRU), one of the stated goals of both the NHS-Galleri and REACH studies. A recent JAMA[24] paper compared the cost effectiveness of colonoscopy vs. a colorectal cancer specific liquid-biopsy (CRC-LB). In brief, this analysis showed CRC-LB in lieu of colonoscopy offered fewer life-year gains (LYG) than colonoscopy alone. While LYG were optimized by CRC-LB used in combination with colonoscopy, the incremental cost effectiveness[25] exceeded $350,000 per LYG (at the current commercial price of $949). That is more than 10x the ICER value for colonoscopy alone (<$30,000 per LYG, at an average procedure cost of

Table 3: Cancers found in PATHFINDER2, by Galleri® or other methods

Increasing need for early detection and treatment

				Not detected by Galleri® *(false-negatives)*							Detected by Galleri® *(true-positives)*						
Cancer Type	**Alt. test available**	**Relative need[i]**	**Total cases**	**Stage I**	**Stage II**	**Stage III**	**Stage IV**	**N/A undet**	**Recur -rent**	**Total**	**Stage I**	**Stage II**	**Stage III**	**Stage IV**	**N/A undet**	**Recur -rent**	**Total**
Lung[ii]	**Yes**	18	12	6	2	1	-	-	2	**11**	-	-	1	-	-	-	**1**
Pancreas	No	12	2	-	-	1	-	-	-	**1**	-	1	-	-	-	-	**1**
Liver / Bile duct	No	4.5	2	-	-	-	-	-	-	**0**	1	-	1	-	-	-	**2**
Colorectal	**Yes**	4.2	3	1	-	-	-	-	-	**1**	-	-	-	2	-	-	**2**
Lymphoma	No	2.0	19	3	1	-	1	2	-	**7**	4	4	1	2	-	1	**12**
Stomach / Intestine	No	2.0	1	-	-	-	-	-	-	**0**	1	-	-	-	-	-	**1**
Breast	**Yes**	1.9	22	10	3	1	-	-	3	**17**	-	-	-	-	-	5	**5**
Ovary	*Yes*	1.4	2	-	-	1	-	-	-	**1**	-	-	1	-	-	-	**1**
Prostate	*Yes*	1.1	20	7	9	1	-	-	1	**18**	-	-	-	1		1	**2**
Head & Neck	No	1.0	2	-	-	-	-	-	-	**0**	-	1	-	1	-	-	**2**
Brain	No	0.7	4	-	-	-	-	2	2	**4**	-	-	-	-	-	-	**0**
Kidney	No	0.6	1	-	-	1	-	-	-	**1**	-	-	-	-	-	-	**0**
Uterus	*Yes*	0.6	4	1	-	1	-	-	1	**3**	1	-	-	-	-	-	**1**
Bladder	No	0.4	3	1	1	-	-	-	1	**3**	-	-	-	-	-	-	**0**
Cervical	Yes	0.4	0	-	-	-	-	-	-	**0**	-	-	-	-	-	-	**0**
Sarcoma	No	0.3	1	-	-	-	-	-	-	**0**	-	1	-	-	-	-	**1**
Melanoma	No	0.2	8	4	2	-	1	1	-	**8**	-	-	-	-	-	-	**0**
Skin (non-melanoma)	No	0.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thyroid	*Yes*	<0.1	6	3	1	-	-	2	-	**6**	-	-	-	-	-	-	**0**
Leukemias	No	N/A[iii]	4	-	-	-	-	1	1	**2**	-	-	-	-	2	-	**2**
Other heme cancers	*No*	N/A[iii]	6	-	-	3	-	-	-	**3**	-	-	-	-	3	-	**3**
Total			**122**	*36 (42%)*	*19 (22%)*	*10 (12%)*	*2 (2%)*	*8 (9%)*	*11 (13%)*	**86**	*7 (19%)*	*7 (19%)*	*4 (11%)*	*6 (17%)*	*5 (14%)*	*7 (19%)*	**36**

Alternate test available and USPSTF endorsed
Alternate test available, not USPSTF endorsed

Notes: (i) Value assigned from product: [5-yr survival odds ratio for local vs regional disease], [1-(share local at diagnosis)], [Annual deaths], and 10^6. (ii) Includes mesothelioma(iii) Leukemia and other hematologic malignancies are not staged in the same way as solid cancers; therefore the relative need cannot be scored with our approach.

$1,120);[26] the price of CRC-LB must drop to ~$350 to approach equivalent ICER value to colonoscopy.

However, since Galleri®'s intended use is across many cancers, a true cost-analysis must go beyond colorectal cancer and incorporate the impact across multiple cancers (and surely that is the driver behind the current price-tag). And herein lies the challenge of a broad, pan-cancer approach: many of the rare cancers occur at such low prevalence that the positive-predictive value of the test is inherently low (i.e., many more false- than true-positives). As a result, many full-diagnostic workups ordered will never yield a cancer to treat yet incur substantial HCRU - potentially driving much more added cost than justified by identified cancers and saved lives.

Concluding thoughts

Until the readout from larger studies become available, it is simply too early to comment on whether Galleri® (or other pan-cancer tests) should become a part of routine care. However, it seems surprising that developers have taken the broad, pan-cancer approach, despite vastly different levels of unmet need, different risks of false-positives and inherent predictive value across cancers. Why not first develop a test specific to one of the more lethal asymptomatic diseases (e.g., pancreatic or liver cancer)? Given the rate at which these cancers are found "too late", and no minimum sensitivity / specificity bar is set by alternate screening methods.

While pan cancer detection may sound revolutionary, and likely appeals more strongly to investors and the general public, getting it implemented is sure to be much harder than tests targeted to a few high-need cancers. When we think of overall impact on outcomes, there is a non-zero risk the pan-cancer approach is net-negative - because despite catching some cancers earlier, it could also worsen outcomes for the most common cancers (e.g., lung breast, colorectal) and adds to total HCRU in follow-up testing for the least-common cancers.

Endnotes

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