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List of abbreviations

BMJ	British Medical Journal
CMS	Centers for Medicare & Medicaid Services
CCGA	Circulating Cell-free Genome Atlas
cfDNA	Circulating Free DNA
CLIA	Clinical Laboratory Improvement Amendments
DMC	Detroit Medical Center
FIT	Fecal Immunochemical Test (used in colorectal cancer screening)
BUCAH	The five largest insurers: Blue Cross/Blue Shield, UnitedHealthcare, Cigna, Aetna, Humana
FDA	Food and Drug Administration
GLP-1	Glucagon-like Peptide-1
TRICARE	Health care program of the U.S. Department of Defense
LDT	Lab Developed Test
LDCT	Low-Dose Computed Tomography (used in lung cancer screening)
MCED	Multi-Cancer Early Detection
NPV	Negative Predictive Value
PIT	Patient-Initiated Telemedicine
PPV	Positive Predictive Value
SOC	Standard of Care
CCGA3	Sub-Study of GRAIL's CCGA study
TAM	Total Addressable Market
NHS	UK's National Health Service
USPSTF	United States Preventive Services Task Force

List of references

All citations, references, and sources are publicly available. Annual reports and other company documents were obtained through the respective issuer's website, regulatory filings, and commercial registries. Documents are cited as follows:

< company name / author > < year of publication / business year >, < document title >, < page >

Some documents, articles and SEC filings were retrieved through direct URLs, and those are quoted directly.

The phrase "company data" indicates that we aggregated the specific metrics from one or several respective regulatory filings.

List of figures

If not stated otherwise, all figures are obtained through the quoted references in the footnotes and can be found in the respective source.

GRAIL: Why Galleri Will Fail the Real Test: Regulatory Approval and Widespread Commercialization All But Impossible

Executive Summary

We are short GRAIL, Inc. (NASDAQ: GRAL), because, in our opinion, the company's overly ambitious approach to cancer screening has created **insurmountable regulatory roadblocks**. Additionally, leadership's **persistent disregard for expert advice** and a dysfunctional corporate culture have led to significant operational missteps, disappointing sales, and **looming financial distress.**

In the end, we believe GRAIL's cancer detection test is backed by data that is just enough to create investor hype, but far too weak to convince experts, regulators, or insurers of its clinical utility.

In our opinion:

- **Insurance coverage hinges on a series of contingent regulatory approvals and success is improbable.**

  GRAIL is a commercial-stage company currently trying to bring its Multi-Cancer Early Detection (MCED) test to market. MCED tests aim to detect multiple cancers simultaneously, often from a single blood sample. GRAIL claims its Galleri test can identify over 50 types of cancer—significantly more than any competitor. The company's viability depends on securing insurance coverage for its test.

  While the company is currently selling the test as a Lab Developed Test (LDT), Galleri has neither FDA approval nor widespread coverage. We believe investors are unrealistically optimistic about the company's prospects, with the bull case hinging on a precarious chain of contingencies required for widespread commercialization: FDA approval → USPSTF guideline inclusion → CMS reimbursement → Private payor coverage. Each step is uncertain on its own and collectively improbable.

  A worldwide leading cancer expert and former executive told us *"that FDA approval does not translate into guideline approval, does not translate into screening recommendations, nor does it translate into coverage."* The reason for this is simple: GRAIL must demonstrate clinical utility—specifically mortality reduction—to be included in USPSTF guidelines, which in turn is the pathway to getting insurance coverage.

  However, GRAIL's registrational trials, NHS-Galleri and PATHFINDER 2—are not designed to show real mortality reduction. GRAIL's acting CFO even acknowledged in March 2025: "*We're not going to have mortality data because it would take 10 years and probably $0.5 billion to get there."* Instead, PATHFINDER 2 and NHS-Galleri focus on safety and effectiveness, just meeting the minimum bar for FDA approval, while NHS-Galleri is allegedly designed to evaluate stage shifts as well.

  Bulls often point to the recently reintroduced MCED bill as a path to bypass regulatory hurdles and enable broad insurance coverage by 2028. However, the fine print reveals that coverage would only apply to a narrow segment of Medicare enrollees—specifically, those aged 67 and younger in 2028. Furthermore, the bill stipulates that Medicare would only cover the MCED test if the CMS determines that adoption is appropriate.

- **Anticipated FDA approval for 50+ cancers can be categorically excluded.**

  According to leading experts and former employees, an FDA approval for 50+ cancers is improbable. An Illumina expert testified that Galleri has only been shown to detect seven types of early-stage cancer, not the marketed 50+ cancers. Former GRAIL scientist told us that if Galleri ever gets FDA approval, the approved test will be curtailed to a few niche cancers: *"I don't believe they will approve all 50 at all. […] they're going to get breast and prostate out of there […]."*

  GRAIL's former CEO has admitted under oath that GRAIL's Galleri Test is not as sensitive as the SOC screening methods. Our analysis of GRAIL's data shows high early-stage sensitivity in only six rare cancers, with prevalence rates ranging from 0.019% (liver/bile duct) to 0.144% (colon/rectum)—significantly lower than more common cancers like prostate (0.61%) and breast (0.67%).

  These low-prevalence cancers underscore Galleri's role as a niche test. At best, if GRAIL were to get FDA Approval, it would be limited to a significantly smaller subset of cancers. A curtailed Galleri test will re-position it as a niche diagnostic application rather than a widespread screening tool, raising serious doubts about its commercial potential and cost-benefit surplus for insurers.

  While the refined Galleri test reports a 43.1% PPV, our in-depth analysis discovered that it was overfitted to hematologic malignancies (blood cancer)—resulting in a decline in PPV from 46.3% to 39.6% for solid tumors, which represent nearly 91% of nationwide cancer prevalence. This trade-off further erodes the cost-benefit surplus of GRAIL's MCED test for CMS and private payors.

- **Payors have designated Galleri as *"unproven," "not medically necessary,"* and *"not covered."***

  A former GRAIL sales manager told us that the Big 5 insurers have designated Galleri as *"investigative and experimental (I&E),"* a classification that—when tied to CPT code 81479—effectively blocks reimbursement: *"If you get that designation in their claim system, they're not paying for the test, no matter what."* They added, *"That's a killer from a testing standpoint. You want to avoid I&Es."*

  We reviewed the current BUCAH medical policies and discovered that Aetna labeled the Galleri test *"experimental, investigational, or unproven,"* UnitedHealthcare called it *"not medically necessary,"* and Blue Cross deemed it *"investigational; therefore, not covered."* Both Humana and Cigna listed it as *"not covered,"* with Cigna applying this to all cfDNA analyses.

  Even TRICARE's recently announced Galleri "coverage" falls into this category, as GRAIL's own ordering guide confirms the test is billed under the scrutinized CPT code 81479. TRICARE's reimbursement is significantly limited, conditional, and subject to strict preauthorization—reflecting administrative ambiguity rather than meaningful market adoption.

- **GRAIL's comparison to standard screening tools is materially misleading.**

  At a recent Jeffries conference, GRAIL's CEO trumpeted that *"the positive predictive value for Galleri in the population -- in the study population was 43%, which is an order of magnitude higher than leading single cancer screening tests."* GRAIL is repeating materially misleading claims about its PPV in comparison to existing screening methods.

GRAIL contrasts its touted 43.1% PPV with far lower figures from established single-cancer tests (e.g., FIT, LDCT, mammography) while ignoring critical differences in study design, population, and prevalence. When recalculated using CCGA3 data and CDC prevalence rates, for example, Galleri's PPV drops to 5.17% for lung cancer (vs. 3.8% in LDCT) and 3.27% for breast cancer (vs. 4.4% in mammography)—figures that directly undercut the company's narrative of diagnostic superiority.

- **Experts and former scientists ring the alarm on GRAIL**

  A leading expert at MD Anderson Cancer Center and former scientific advisor to GRAIL warned the company that its trial design was *"fundamentally flawed,"* and later concluded that the company surrounded itself with *"people who had drunk the Kool-Aid."* Other leading oncology experts questioned why the Galleri test—described as showing *"so little promise"* in earlier trials—was being tested on UK patients.

  A BMJ article uncovered internal emails suggesting "behind closed doors" agreements, further fueling doubts about the trial's legitimacy. The Chair of the UK's National Screening Committee voiced *"serious concerns"* about the NHS-Galleri trial and its cost-benefit surplus.

- **GRAIL's toxic culture: former staff cite executive hubris and questionable decision-making.**

  A former high-ranking manager told us *"I think that the executive team was not a well-functioning team at all. I think decisions were made for reasons other than what's the best way to show this test works."*. Additionally, all former employees we spoke to described the corporate culture as *"toxic," "terrible," and "challenging."*

  According to former staff, *"The executive team at GRAIL was rated the worst-performing unit within GRAIL for three straight years. The feedback given was very specific."* In the fourth year, management stopped disclosing its internal survey results, with one former interpreting *"But it was one of the worst cases of hubris ever, like: yeah, we don't really care, and you don't count."*

  Moreover, three lawsuits have alleged a toxic workplace culture marked by racism and sexism, portraying GRAIL as a fraternity-like environment—complete with free alcohol at all times and drinking during sales strategy meetings.

- **GRAIL's valuation hinges on cash reserves amid regulatory uncertainty**

  GRAIL's actual sales have massively underperformed projections—achieving only 10% of the original 2020 revenue estimates ($75M in 2023 vs. projected $462M, and $108M in 2024 vs. projected $892M). Losing hundreds of millions per year, GRAIL is burning through the Illumina-funded cash position at a rate that calls into question its runway.

  Management expects GRAIL's cash reserves to last until 2028. However, we believe that by then, reimbursement and broad market adoption will still be absent. Therefore, GRAIL's fair value should remain anchored to its projected cash reserves through 2025—approximately $14.28 per share.

1. GRAIL's Bull Case Relies on Loopholes and Unrealistic Assumptions

Established in September 2015 by executives from San Diego-based biotech firm Illumina, GRAIL derives its name from its ambitious aim: to develop nothing less than a blood-based 'liquid biopsy' test capable of detecting multiple cancers in asymptomatic individuals—a goal often referred to as the 'Holy Grail of Oncology.'[1]

GRAIL claims that its proprietary Galleri MCED test, based on a proprietary methylation platform, can identify more than 50 cancer types before symptoms become apparent.[2] Bullish investors see a compelling proposition, as reliable early-stage cancer detection using one single blood test would represent a breakthrough in the healthcare sector—and for humanity overall, helping to avoid millions of cancer deaths over the coming decades.[3] According to sell-side research, the market opportunity would be enormous: over 100 million people in the U.S. alone could benefit from this kind of easy, early screening solution.[4]

Despite the promise, GRAIL's journey toward delivering on that potential has been far from smooth.

Initially, Illumina launched GRAIL with a $100 million Series A round in January 2016.[5] The company started to conduct clinical studies, such as the Circulating Cell-free Genome Atlas (CCGA) study, and develop its signature Galleri multi-cancer early detection (MCED) test.[6] By February 2017, GRAIL had held a successful $900-million Series B financing round and was spun off from Illumina, gaining operational independence.[7] After raising another 1.9 billion in funding, reaching a $4-billion valuation in 2020, and preparing for an IPO, GRAIL was surprisingly reacquired by Illumina in 2021—for a cool $7.1 billion thanks to Illumina's claims of an acceleration FDA approval and rapid commercial roll-out for Galleri.[8] Immediately, the FTC and EU anti-trust regulators stepped in, investigating the deal.[9] [10] However, without waiting for the FTC's and EU's approval, Illumina closed the deal, leading to a lengthy and expensive FTC trial and a $471 million fine from the EU.[11] [12] **Ultimately, following an EU order to sell GRAIL, and a disastrous $4.7 billion impairment of GRAIL's associated goodwill, Illumina decided to divest.**[13] **In 2024, GRAIL was spun back off** again as Illumina maintained a 14.5% stake. Since GRAIL's acquisition in 2021, Illumina's share price plummeted from around $500 to $84, wiping out billions in shareholder value.

While corporate turbulence unfolded, the Galleri test has also faced large obstacles: GRAIL hasn't managed to secure approval for Galleri from the Food & Drug Administration (FDA), and this will only be the first step on the regulatory path towards roll-out.[14] Admittedly, GRAIL is now badly behind schedule

[1] https://www.theguardian.com/society/2018/jun/01/doctors-welcome-possible-holy-grail-of-cancer-research
[2] https://grail.com/multi-cancer-early-detection/
[3] Canaccord Equity (2025), Blazing a trail in the lucrative MCED market while managing cash burn; initiating at BUY and $32 PT, pg. 1
[4] Wolfe Research (2024), The Quest For The GRAIL Warrants Respect But Also A Ton Of Time & Money; Initiate at PP, pg. 11
[5] Wolfe Research (2024), The Quest For The GRAIL Warrants Respect But Also A Ton Of Time & Money; Initiate at PP, pg. 9
[6] Wolfe Research (2024), The Quest For The GRAIL Warrants Respect But Also A Ton Of Time & Money; Initiate at PP, pg. 9
[7] https://storage.courtlistener.com/recap/gov.uscourts.casd.772025/gov.uscourts.casd.772025.46.0.pdf, pg. 57
[8] https://www.ft.com/content/3603bef0-0c75-4744-bd83-4602b96c9762
[9] https://www.ftc.gov/news-events/news/press-releases/2021/03/ftc-challenges-illuminas-proposed-acquisition-cancer-detection-test-maker-grail
[10] https://ec.europa.eu/commission/presscorner/detail/en/ip_21_3844
[11] https://www.reuters.com/markets/deals/eu-top-court-backs-illumina-fight-against-eu-probe-into-grail-deal-2024-09-03/
[12] https://www.medtechdive.com/news/Illumina-SEC-ends-Grail-investigation-Q1/747691/
[13] https://www.reuters.com/business/healthcare-pharmaceuticals/illumina-take-147-bln-goodwill-impairment-charge-related-grail-q2-2024-06-27/
[14] https://www.bamsec.com/transcripts/a25fbda4-263d-4960-a377-3f8d82262758

here, having promised the submission for its FDA approval as a first step for 2023, then 2024, and now 2026.[15] [16] [17]

After the FDA approval, GRAIL will need to provide the United States Preventive Services Task Force (USPSTF) with evidence of Galleri's clinical utility, and only then can it progress for Medicare reimbursement.[18] [19] However, bullish investors point to efforts to bypass the stubborn regulators and speed things up by introducing a bill to Congress that would allow Medicare to cover MCED tests without USPSTF recommendations.[20] [21] Until then, Galleri is being used by cash-pay customers in the private, personal, and concierge segments, generating negligible revenue while the company waits for its breakthrough.[22]

2. The Wrong Path to Validation: GRAIL's Flawed Clinical Trial Design

We think the **bull case is unrealistically optimistic.** It hinges on a series of contingent regulatory approvals and recommendations, all occurring in a sequence exactly as GRAIL desires: First, the company must get FDA approval. If approval occurs, there has to be a favorable USPSTF recommendation (or for any legislative workaround to be feasible) for the Center for Medicare & Medicaid Services (CMS) to determine widespread reimbursement.[23] We believe, contrary to both the company's communications and many investors' expectations, GRAIL securing blanket FDA approval for Galleri with a label that covers 50+ cancers is not simply a matter of time. **In our opinion, GRAIL's approach to clinical trials makes Galleri clearing this first hurdle seem like a low probability.**

GRAIL is currently relying on two currently ongoing clinical studies to provide registrational data for FDA submission: the PATHFINDER-2 and NHS-Galleri studies.[24]

2.1. GRAIL's Best-Case Scenario: Narrow Approval for a Handful of Cancers

Data from the NHS Galleri trial is not expected until early 2026 at the earliest, and final results from PATHFINDER 2 are unlikely to be available before early 2028 (although the company claims they will provide interim data later this year).[25] [26] Nevertheless, investors have largely given GRAIL the benefit of the doubt, buying into the stock on the belief that Galleri will ultimately receive FDA approval in 2027. **Many former employees and experts we spoke to are very skeptical that GRAIL would even get FDA approval.** In our opinion, it has been internally understood for years that GRAIL would face significant challenges demonstrating effectiveness to the FDA, as **its Galleri test consistently underperforms on a per-cancer basis compared to existing standard-of-care (SOC) screening tests—a point confirmed by testimony from GRAIL's former CEO Hans Bishop,** who acknowledging the superiority of current SOC tests.[27]

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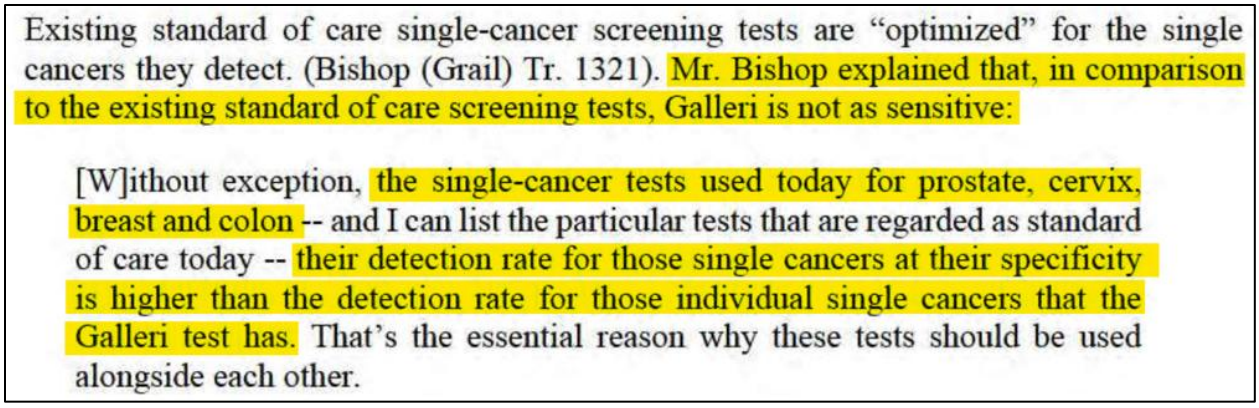
[15] https://www.fiercebiotech.com/medtech/illumina-completes-grail-acquisition-regulators-be-damned
[16] https://cancerletter.com/clinical/20241025_1/
[17] https://www.bamsec.com/transcripts/aeefb91a-ce75-4be2-8002-53ad47de4f6a
[18] https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual/procedure-manual-appendix-i
[19] https://www.bamsec.com/transcripts/a25fbda4-263d-4960-a377-3f8d82262758
[20] The bill states that coverage is limited Coverage is limited to those under a certain age (age 68 in 2028, increased by one year every year thereafter) and to one test every 11 months. Because Medicare coverage only starts at 65, it's a very small addressable market for GRAIL.
[21] https://moskowitz.house.gov/posts/medicare-mced-tests
[22] https://www.fiercebiotech.com/medtech/grail-launches-its-50-cancer-galleri-blood-screening-test
[23] https://www.cms.gov/medicare/prevention/prevntiongeninfo/medicare-preventive-services/mps-quickreferencechart-1.html
[24] https://www.bamsec.com/transcripts/aeefb91a-ce75-4be2-8002-53ad47de4f6a
[25] https://clinicaltrials.gov/study/NCT05155605
[26] https://www.bamsec.com/transcripts/aeefb91a-ce75-4be2-8002-53ad47de4f6a
[27] https://www.ftc.gov/system/files/ftc_gov/pdf/D09401CCPostTrialFOFCOL.Part1_.pp_.1-392.pdf, pg. 79



Existing standard of care single-cancer screening tests are "optimized" for the single cancers they detect. (Bishop (Grail) Tr. 1321). Mr. Bishop explained that, in comparison to the existing standard of care screening tests, Galleri is not as sensitive:

> [W]ithout exception, the single-cancer tests used today for prostate, cervix, breast and colon -- and I can list the particular tests that are regarded as standard of care today -- their detection rate for those single cancers at their specificity is higher than the detection rate for those individual single cancers that the Galleri test has. That's the essential reason why these tests should be used alongside each other.

Figure 1 GRAIL's former CEO testified that Galleri is not that sensitive in comparison to existing SOC screening methods, source: FTC

One former sales manager estimated **Galleri's chances of FDA approval at just 5%.** Others voiced **concern that the NHS Galleri trial is being conducted in the UK**, while the FDA typically requires data that is representative of the U.S. population for approval:

> *"[…] **Putting in foreign patients, I think, that is also a big issue** because it has to be the same geographical race and ethnicity makeup as the target population, **the intended population in the US. UK is not that.** I don't know what GRAIL is going to do about that. […]"*

Several current and former employees also noted that even if GRAIL were to secure FDA approval, it would likely not cover all 50+ cancers that have been marketed:

> *"[…] **I don't think it's going to be a blanket approval across all cancers.** That's the biggest tricky part, because some of these cancers are so low incidence that even if you run population-scale trials, it's really difficult to get enough patients to create a package. […]"*

A former scientist was somewhat more optimistic, assigning a greater than 50% chance of FDA approval—but immediately qualified that this would not apply to all 50 cancer types:

> *"[…] FDA approval probability of success, I'd give it definitely above 50%. **Certainly not for all 50 cancers,** and it may vastly depend on who else is in CDER at the FDA. […]"*

Another former scientist and leading expert indicated that GRAIL will likely have to exclude certain common cancers, such as breast and prostate cancer, from its test:

> *"**[…] I don't believe that they will approve all 50 at all. I think they're going to have to pick and choose.** Immediately, **they're going to get breast and prostate out of there** like we were discussing. But what that label will look like and **what the FDA will let them do is a big question.** […]"*

This view is further supported by testimony from an expert at GRAIL's former parent company, Illumina, during an FTC trial.[28] The expert admitted that Galleri has only been shown to detect seven types of early-stage cancer in the intended-use population of asymptomatic adults—contrary to Illumina's public claims of detecting 50:[29] [30] [31]

> undisputed that Galleri does not yet have FDA approval. Illumina's own expert acknowledged that Galleri has only been shown to detect seven types of early-stage cancer in the intended use-population of asymptomatic adults, not 50 as Illumina repeatedly claims. Op. 54; Tr.

Figure 2 Extract from a FTC filing in the case against Illumina, source: FTC

From this point forward, the content becomes more technical. Please read the Appendix covering concepts like sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), study design types, and more.

Our analysis of the published CCGA3 and PATHFINDER studies reinforces these concerns. Both studies indicate that Galleri performs relatively poorly in detecting common cancers while showing stronger performance in a few rare cancer types.[32] In particular, the CCGA3 study features a chart highlighting impressive sensitivity levels, but **these are aggregated across all clinical stages of cancer, which we believe is highly misleading.[33]**

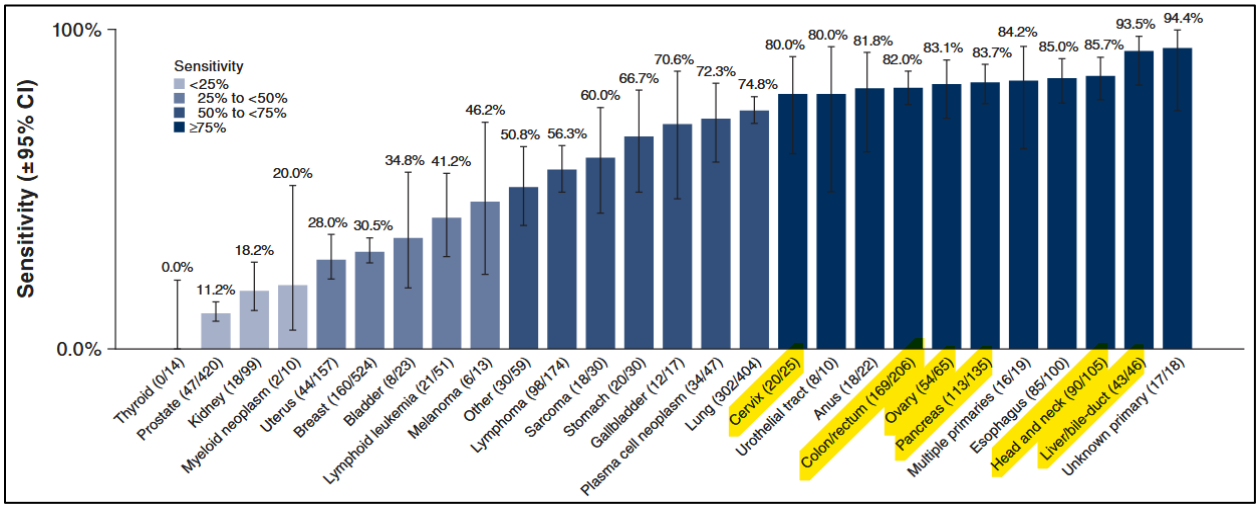


Figure 3 Galleri's sensitivities from the CCGA3 study, source: GRAIL

[28] https://www.ftc.gov/system/files/ftc_gov/pdf/illumina_v._ftc_ftc_brief_public_version_8.4.23.pdf, pg. 28
[29] https://www.ftc.gov/system/files/ftc_gov/pdf/illumina_v._ftc_ftc_brief_public_version_8.4.23.pdf, pg. 28
[30] https://www.ftc.gov/system/files/ftc_gov/pdf/D09401%20-%20COMPLAINT%20COUNSEL_S%20APPEAL%20OF%20THE%20INITIAL%20DECISION%20-%20PUBLIC%20%281%29.pdf, pg. 28
[31] Directly from the FTC documents: *"To date, Grail has presented clinical evidence that the Galleri test can detect seven types of Stage I-III cancer in an asymptomatic screening population. (Cote Tr. 4000-01; RX3041 at 005 (Interim Results of Pathfinder, June 4, 2021) (showing seven cancers as being detected in stages one through three: head and neck, liver/bile duct, lung, lymphoma, ovary, pancreas, and small intestine)"*
[32] https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2821%2902046-9, pg. 8
[33] https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2821%2902046-9, pg. 7

What initially appears impressive quickly unravels upon closer examination. **When sensitivities are analyzed by the cancer stage, Galleri's performance in early-stage detection is far less compelling (see Figure 4 below).**[34] As illustrated below in Figure 4, only a few rare cancers—specifically cervical cancer, colorectal cancer, ovary cancer, head and neck cancer (not brain tumors), bile duct cancer, and pancreatic cancer—demonstrated noteworthy sensitivity at early stages.[35] Among the high sensitivities reported by GRAIL in its CCGA3 study (see Figure 3 and Figure 4), only the cancers marked in yellow are detected reliably in the early stages (for ease of comparison, we followed the same order presented by GRAIL in their chart on overall sensitivity). GRAIL defines early-stage cancer as stages I through III; however, by stage III, the cancer has often begun to spread beyond its original site.[36] [37] In practice, the definition of "early stage" varies by cancer—sometimes limited to stage I (as in pancreatic cancer), and other times including stages I and II (as in head and neck cancer). For this reason, in Figure 4, we bolded the sensitivity values that align with each cancer's specific early-stage definition.[38]

Cancer Stage	Lung	Cervix	Urothelial Tract	Anus	Colon/Rectum	Ovary
All	74.8%	80.0%	80.0%	81.8%	82.0%	83.1%
I *(Early Stage)*	21.9%	58.3%	0.0%	**25.0%**	43.3%	50.0%
I+II *(Early Stage)*	**40.0%**	**70.6%**	**0.0%**	50.0%	**67.1%**	**60.0%**
II	79.5%	100.0%	N/A	75.0%	85.0%	80.0%
III	90.7%	100.0%	N/A	100.0%	87.9%	87.1%
IV	95.2%	100.0%	100.0%	100.0%	95.3%	94.7%

Cancer Stage	Pancreas	Multiple Primaries	Esophagus	Head and Neck	Liver/Bile-duct	Unknown Primary
All	83.7%	84.2%	85.0%	85.7%	93.5%	94.4%
I *(Early Stage)*	**61.9%**	**100.0%**	12.5%	63.2%	**100.0%**	N/A
I+II *(Early Stage)*	61.0%	71.4%	**48.0%**	**72.2%**	81.3%	100.0%
II	60.0%	60.0%	64.7%	82.4%	70.0%	100.0%
III	85.7%	100.0%	94.1%	84.2%	100.0%	50.0%
IV	95.9%	83.3%	100.0%	96.0%	100.0%	100.0%

Figure 4 Selected sensitivities by cancer stage from CCGA3 study, source: NINGI Research, GRAIL, The Lancet

In our opinion, even GRAIL's most frequently cited performance claims warrant serious skepticism. The reported early-stage sensitivities, drawn from the CCGA3 case-control study, do not reflect real-world screening conditions (see Appendix for a refresher on case-control studies).[39] Worse, attempts to validate Galleri's cancer-type-specific efficacy using GRAIL's own PATHFINDER study hit a wall of inconsistent and incomplete data. Supplementary Tables S8A and S8B—the only detailed clinical data disclosed—use conflicting cancer-type classifications, not only relative to each other but also to the CCGA3 study.[40] [41] [42] Further, no data on cancer-specific false positives are disclosed.[43]

[34] https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2821%2902046-9, pg. 8
[35] https://www.annalsofoncology.org/cms/10.1016/j.annonc.2021.05.806/attachment/fc2b365c-9cbb-44dc-a9e8-a728111d6f63/mmc7.docx
[36] https://grail.com/press-releases/grail-presents-initial-results-from-reflection-real-world-evidence-study-of-galleri-multi-cancer-early-detection-mced-test-at-the-early-detection-of-cancer-conference/
[37] https://my.clevelandclinic.org/health/diagnostics/22607-cancer-stages-grades-system
[38] Multiple primaries and cancers of unknown primary origin do not have a defined early stage because: (1) having multiple cancers is inherently more severe than any single late-stage cancer, and (2) when the primary site is unknown, it is not possible to make a meaningful clinical assessment of stage.
[39] https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2821%2902046-9, pg. 10
[40] https://www.annalsofoncology.org/cms/10.1016/j.annonc.2021.05.806/attachment/fc2b365c-9cbb-44dc-a9e8-a728111d6f63/mmc7.docx
[41] https://pmc.ncbi.nlm.nih.gov/articles/instance/11027492/bin/NIHMS1977563-supplement-MMC1.pdf, pg. 14
[42] https://pmc.ncbi.nlm.nih.gov/articles/instance/11027492/bin/NIHMS1977563-supplement-MMC1.pdf, pg. 16
[43] https://pmc.ncbi.nlm.nih.gov/articles/instance/11027492/bin/NIHMS1977563-supplement-MMC1.pdf

Our own analysis of the published data reveals a more sobering reality: **in the PATHFINDER study, Galleri failed to detect a significant number of cancers (see Figure 5 below).**

	New Cancers / Clinical AJCC Stage					Recurrent Cancers				
Sensitivity	**I**	**II**	**III**	**IV**	**NA**	**Local**	**Distant**	**Total**	**True Positives**	**False Negatives**
Colon or rectum	0.00%	**0.00%**	0.00%	100.00%	0.00%	0.00%	0.00%	66.67%	2	1
Kidney	0.00%	**0.00%**	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0	1
Mesothelioma	0.00%	**0.00%**	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0	1
Ovary	0.00%	**0.00%**	50.00%	0.00%	0.00%	0.00%	0.00%	50.00%	1	1
Pancreas	**0.00%**	100.00%	0.00%	0.00%	0.00%	0.00%	0.00%	50.00%	1	1
Bladder	**0.00%**	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0	3
Uterus	**50.00%**	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	1	3
Brain	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0	4
Thyroid	0.00%	**0.00%**	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0	6
Melanoma	0.00%	**0.00%**	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0	8
Lung	0.00%	**0.00%**	100.00%	0.00%	0.00%	0.00%	0.00%	9.09%	1	10
Breast	0.00%	**0.00%**	0.00%	0.00%	0.00%	0.00%	26.32%	22.73%	5	17
Prostate	0.00%	**0.00%**	0.00%	100.00%	0.00%	50.00%	0.00%	10.00%	2	18
Myelodysplastic syndrome	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0	1
Lymphoid leukemia	0.00%	0.00%	0.00%	0.00%	66.67%	0.00%	0.00%	50.00%	2	2
Plasma cell neoplasm	0.00%	0.00%	0.00%	0.00%	33.33%	0.00%	0.00%	33.33%	1	2
Lymphoma	**57.14%**	80.00%	100.00%	66.67%	0.00%	100.00%	0.00%	61.11%	12	7
Intrahepatic bile duct	***0.00%***	*0.00%*	*100.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*100.00%*	*1*	*N/A*
Liver	***100.00%***	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*100.00%*	*1*	*N/A*
Waldenstrom macroglobulinemia	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*100.00%*	*0.00%*	*0.00%*	*100.00%*	*2*	*N/A*
Head and neck	*0.00%*	***100.00%***	*0.00%*	*100.00%*	*0.00%*	*0.00%*	*0.00%*	*100.00%*	*2*	*N/A*
Sarcoma	***0.00%***	*100.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*100.00%*	*1*	*N/A*
Small intestine	***100.00%***	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*100.00%*	*1*	*N/A*
Total	**16.28%**	**26.92%**	**36.36%**	**75.00%**	**31.25%**	**15.38%**	**14.71%**	**29.51%**	**36**	**86**

Figure 5 Sensitivities were calculated, with those defined as early-stage bolded, based on supplementary data from the PATHFINDER study[44], source: GRAIL

Overall, sensitivity for newly diagnosed cancers increases with advancing stage: detection rates were 16.3% for Stage I, 26.9% for Stage II, 36.4% for Stage III, and 75.0% for Stage IV. Yet Galleri's performance in early-stage disease remains markedly limited, undermining its viability as a screening tool.

When comparing the sensitivity data for consistently classified cancer types across both studies (see Figure 4 and Figure 5), it's immediately apparent that **the Galleri test failed to detect early-stage cancers in the PATHFINDER study**—such as pancreatic (stage I) and colorectal cancer (stage II)—**that it had previously identified successfully in the CCGA3 study.**[45] [46] [47]

For recurrent cancers, overall sensitivity was just 29.5%, with local and distant recurrence detection rates of 15.4% and 14.7%, respectively (see Figure 5). Galleri didn't detect several recurrent cancers.[48] **These figures cast doubt on the test's reliability as an addition to post-treatment surveillance methods.** Across all cancer types, the test yielded 36 true positives against 86 false negatives (see Figure 5)—a troubling imbalance, particularly in the context of early and recurrent disease.

In our opinion, the data lead to a clear conclusion: Galleri fails in its primary aim of early detection and cannot be considered a viable supplement to established screening protocols.

[44] Myelodysplastic syndrome, lymphoid leukemia, plasma cell neoplasm, and Waldenstrom macroglobulinemia are not bolded because they follow different staging systems than solid tumors. Brain cancer is also not bolded, as it was identified during the study but is not typically detected by MCED tests due to biological limitations—specifically, the minimal shedding of cfDNA across the blood–brain barrier. The total true positives (TP) count of 36 differs from the 35 used in overall performance metrics, as one cancer signal was classified as intermediate.

[45] https://www.annalsofoncology.org/cms/10.1016/j.annonc.2021.05.806/attachment/fc2b365c-9cbb-44dc-a9e8-a728111d6f63/mmc7.docx

[46] https://pmc.ncbi.nlm.nih.gov/articles/instance/11027492/bin/NIHMS1977563-supplement-MMC1.pdf, pg. 14

[47] https://pmc.ncbi.nlm.nih.gov/articles/instance/11027492/bin/NIHMS1977563-supplement-MMC1.pdf, pg. 16

[48] https://pmc.ncbi.nlm.nih.gov/articles/instance/11027492/bin/NIHMS1977563-supplement-MMC1.pdf, pg. 16

Despite repeated references to the 43.1% positive predictive value (PPV) reported in the PATHFINDER study, GRAIL has yet to release the full dataset of the refined test—specifically, the breakdown of false positives and false negatives by cancer type.[49] To date, the company has disclosed only the per-cancer true positive counts for the refined test version.[50]

This omission begs critical questions: how does the test perform across individual cancers, particularly those where a false positive could lead to burdensome and invasive follow-up procedures such as CT scans or biopsies? The tumor type–level analysis possible from the scattered data in the PATHFINDER documents already reveals a critical flaw: **the refined Galleri test, designed to improve specificity for blood cancers, suffers from a diminished PPV (dropping from 46.3% to 39.6%; see Figure 6 below) for solid tumors**—even though solid tumors account for nearly 91% of all prevalent cancers nationwide.[51]

Tumor type	**Solid tumors**		**Blood cancers**		**Overall**	
Galleri test	*Study version*	*Refined version*	*Study version*	*Refined version*	*Study version*	*Refined version*
True Positives	19	19	16	6	35	25
False Positives	22	29	35	4	57	33
PPV	**46.3%**	**39.6%**	**31.4%**	**60.0%**	**38.0%**	**43.1%**

Figure 6 True Positives, False Positives, and PPV for solid tumors, hematologic malignancies (blood cancers), and all tumors, source: The Lancet

This raises concerns that the refined MCED test may offer less clinical utility where it is needed most—in detecting solid tumors accurately—while also risking unnecessary follow-up procedures due to lower PPV in these cases. In our opinion, **the improvement in overall PPV comes at the expense of a diminished overall cost-benefit surplus, an objective that is as equally important to regulators as PPV itself.**

Equally pressing is the question of false negatives—cases in which the test fails to detect cancer, especially more aggressive recurrent forms—potentially resulting in diagnoses at far more advanced stages, when treatment options may be more limited and outcomes significantly worse. An analysis is not possible, as GRAIL chose not to disclose false negative data by individual cancer type and stage for the refined test.[52]

In our opinion, the drop in overall sensitivity to just 20.8%, coupled with a decline in negative predictive value—signaling an increase in false negatives—makes it **a matter of fiduciary responsibility to release the full dataset, particularly when such performance metrics are routinely highlighted in investor communications.**[53] Without transparency at the cancer-specific level, the clinical implications of both types of error remain obscured.

We think this disconnect points to a deliberate lack of transparency from a company making bold commercial claims about a product that targets one of the most high-stakes markets in healthcare. In our opinion, GRAIL's selective disclosure and shifting performance benchmarks fall well short of accepted clinical and investor communication standards.

We strongly encourage independent replication efforts—because when you try to reconstruct the numbers from the published data, what you find isn't a breakthrough in early cancer detection. You find red flags.

[49] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01700-2/
[50] https://pmc.ncbi.nlm.nih.gov/articles/instance/11027492/bin/NIHMS1977563-supplement-MMC1.pdf, pg. 28
[51] https://gis.cdc.gov/Cancer/USCS/#/NationalPrevalence/
[52] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01700-2/
[53] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01700-2/

Our findings support the skepticism expressed by **former employees, who believe that significantly fewer than the 50+ cancers currently marketed will be included in any eventual FDA approval.** In our opinion, Galleri, if approved at all, would likely receive labeling only for a limited subset of cancers—those with sufficiently high sensitivity and positive predictive value to demonstrate clinical validity. We believe **the curtailed Galleri test may only include the six yellow-highlighted cancer types** shown in Figure 4.

	Pancreas	Cervix	Head and Neck	Liver/Bile-duct	Ovary	Colon/Rectum	Combined	Total
5-year prevalence (CDC)	0.021%	0.029%	0.032%	0.019%	0.039%	0.144%	0.284%	1.76%
in % of total prevalence rate	1.193%	1.648%	1.818%	1.080%	2.216%	8.182%	16.136%	100.00%

Figure 7 Five-Year Prevalence rates for GRAIL's detected early-stage cancer types, source: CDC

However, data from the CDC reveals that **this curtailed Galleri test would represent just 16.2% of all cancers prevalent nationwide (see Figure 7 above),** with prevalence rates ranging from 0.019% (liver/bile duct) to 0.144% (ovary)—significantly lower than more common cancers like prostate (0.61%) and breast (0.67%).[54] We want to highlight that without Colorectal cancer, the represented prevalence would drop to 7.95%.

Even in the unlikely scenario that GRAIL secures FDA approval in 2027 (submission in 2026), we anticipate this would be for a restricted subset of cancers. **Such a limited approval would drastically reduce GRAIL's total addressable market (TAM) shifting Galleri's role from a broad-based screening platform to a narrowly focused diagnostic tool—becoming the antithesis of its unique proposition and significantly weakening commercial potential.**

2.2. GRAIL's Flagship Trials Fall Short of Demonstrating Clinical Utility

For a product like GRAIL's Galleri test to receive FDA approval, it must demonstrate safety and effectiveness through consistent, reliable data.[55] GRAIL aims to meet this standard with its PATHFINDER 2 and NHS-Galleri studies, both of which list safety and effectiveness as their primary outcome measures (three years after NHS-Galleri enrollment, GRAIL has started telling investors that the NHS-Galleri trial's primary endpoint is a stage shift reduction).[56] [57] [58] [59] **While these studies align with the FDA's baseline requirements,** they primarily serve to satisfy the minimum threshold for approval.[60] Beyond this point, **advancing the Galleri test further**—whether for broader clinical adoption, reimbursement, or market differentiation—**will require additional data that go beyond the scope of these initial studies.**[61]

And to be clear: FDA approval does not mean that USPSTF, CMS, or private payors will then also approve Galleri or cover the costs. This was also confirmed to us by a former leading GRAIL scientist:

> *"[…] I want to make sure that I'm super clear* ***that FDA approval does not translate into guideline approval, does not translate into screening recommendations, nor does it translate into coverage.*** *Those types of things are*

[54] https://gis.cdc.gov/Cancer/USCS/#/NationalPrevalence/
[55] https://www.fda.gov/medical-devices/premarket-approval-pma/pma-application-contents#ssed
[56] https://clinicaltrials.gov/study/NCT05155605
[57] https://www.nhs-galleri.org/about-the-trial
[58] We want to emphasize that on GRAIL's own NHS-Galleri website, the aim of the trial is to *"see how well the Galleri blood test works in the NHS. The aim of the trial is to see if using the Galleri test alongside existing cancer screening can help to find cancer early."* Only three years after enrollment, GRAIL has started telling investors that trials primary endpoint is a stage shift reduction.
[59] https://www.england.nhs.uk/2021/09/nhs-launches-world-first-trial-for-new-cancer-test/
[60] https://www.fda.gov/medical-devices/premarket-approval-pma/pma-application-contents#ssed
[61] https://cancerletter.com/clinical/20241025_1/

going to be really important from a financial perspective, from a company perspective. […]"

The regulatory hurdles that GRAIL must overcome are complex and, as we understand, in three out of four cases require different clinical data to that which NHS-Galleri and PATHFINDER 2 will produce:

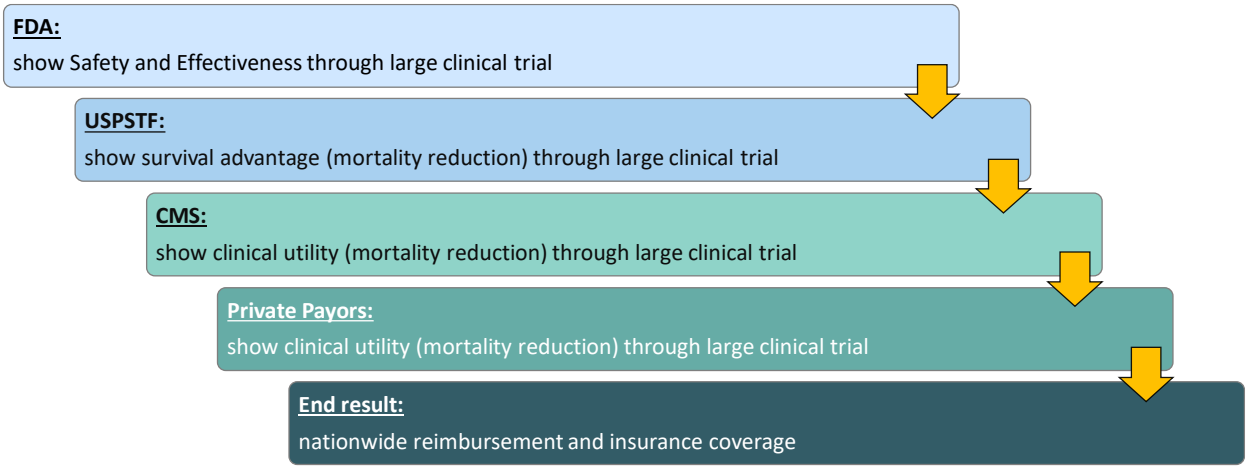


Figure 8 Contingent regulatory approvals until Galleri receives insurance coverage, source: FDA, USPSTF, ACA, NINGI Research

We find that any discussion by experts about the clinical utility of MCED tests always focuses on mortality reduction.[62] The FDA, or more precisely the responsible Center for Devices and Radiological Health, does not require proof of mortality reduction for the pre-market approval of a medical device.[63] Mortality reduction is critical in showing utility to get on USPSTF guidelines, which in turn informs Medicare, the largest reimbursement player, and other commercial payors.[64]

This is why experts and industry insiders always assume that large-scale clinical studies are used to immediately prove mortality reduction to the FDA, instead of just 'safety and effectiveness'.

GRAIL has instead designed its two extremely expensive PATHFINDER 2 and NHS-Galleri studies to only meet the low bar required by the FDA.

The problem with this, however, is that if the FDA approves Galleri, the studies and data cannot be used for further regulatory recommendations and guidelines. Several former employees have confirmed to us that every single body after the FDA requires proof of clinical utility through mortality reduction:

"[Private health insurance companies] going to review it, so they don't have to pay for it if they don't like it. Right now, given the database, they don't like it, same as the FDA, same as USPSTF. ***They all have the same clinical hurdle that we got to address, and that's clinical utility data.*** *[…]"*

GRAIL has no study that will prove this outcome, and according to GRAIL's current CFO, there will never be such a study.[65]

[62] https://www.fda.gov/media/175307/download, pg. 13
[63] https://www.fda.gov/media/175307/download, pg. 13
[64] https://www.bamsec.com/transcripts/57abf23a-6d9e-4090-9a6d-11dbadda9f54
[65] https://www.bamsec.com/transcripts/57abf23a-6d9e-4090-9a6d-11dbadda9f54

The company's Chief Financial Officer was very explicit about this issue at a recent investor talk in March 2025:[66]

> *"[…] **We don't have -- we're not going to have mortality data because it would take 10 years and probably $0.5 billion to get there**. And by then, the technology is no longer likely relevant. […]"*

Instead of conducting trials that conform to the gold standard—using mortality reduction as the primary endpoint—**GRAIL has opted for novel surrogate endpoints**, **such as a reduction in late-stage diagnoses (stage shift),** citing its belief that these are *"thought by experts to be a prerequisite for a mortality reduction."* [67] [68] Allegedly, GRAIL is running two trials focused on demonstrating stage shift. In 2024, following criticism of its NHS-Galleri trial, GRAIL abruptly informed investors and the public that stage shift was the trial's primary endpoint, despite prior statements from both GRAIL and the NHS describing the trial as aiming *"to see how well the test works in the NHS."*[69] This year, GRAIL launched a study called 'REACH', also intended to demonstrate stage shift, with the earliest estimated primary completion date currently set for September 2030.[70]

However, many experts disagree about the novel endpoint—like Dr. David Carr, Assistant Professor and Medical Director at DMC Hospital's Molecular Genetic Diagnostic Laboratory, who has called GRAIL's substitute endpoint *"problematic"*, stating that *"[…] it is a surrogate measure of efficacy—and surrogates are often misleading."* [71] **During an FDA-led expert panel, several leading experts, professors, and cancer institute directors underscored the need for mortality reduction as the primary endpoint.[72]** In parallel, they raised concerns over the reliability and clinical relevance of surrogate measures such as stage shift.[73] [74]

According to a former GRAIL scientist, **no surrogate endpoints are currently acceptable to the USPSTF,** as it is legally required to base any screening recommendation on demonstrated survival benefit:

> *"[…] They decide, but **they have a rule**, and this goes back to the Affordable Care Act, that **you have to show a survival advantage in order to be approved for screening.** That's the big issue now. […]"*

Predictably, bullish investors will point to the recently introduced MCED bill, designed to bypass the USPSTF's recommendation process.[75] While the bill is often cited as a bullish signal, a close read of **the MCED bill reveals that the USPSTF recommendation would be bypassed only for a limited subset of Medicare enrollees—specifically, those aged 67 and younger in 2028 (see Figure 9 below).[76]**

[66] https://www.bamsec.com/transcripts/57abf23a-6d9e-4090-9a6d-11dbadda9f54
[67] https://www.bamsec.com/transcripts/57abf23a-6d9e-4090-9a6d-11dbadda9f54
[68] https://grail.com/stories/grail-statement-on-the-new-york-times-multi-cancer-early-detection-story/
[69] https://www.england.nhs.uk/2021/09/nhs-launches-world-first-trial-for-new-cancer-test/
[70] https://clinicaltrials.gov/study/NCT05673018
[71] https://journals.sagepub.com/doi/10.1177/09691413211059638
[72] https://www.fda.gov/media/175307/download, pg. 13
[73] https://www.fda.gov/media/175307/download, pg. 12
[74] https://www.fda.gov/media/175308/download, pg. 58
[75] https://www.congress.gov/bill/118th-congress/senate-bill/2085
[76] https://www.congress.gov/bill/119th-congress/house-bill/842

Introduced in House (01/31/2025)

Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act

This bill allows, beginning in 2028, for Medicare coverage and payment for multi-cancer early detection screening tests that are approved by the Food and Drug Administration and that are used to screen for cancer across many cancer types, if the Centers for Medicare & Medicaid Services determines such coverage is appropriate. Coverage is limited to those under a certain age (age 68 in 2028, increased by one year every year thereafter) and to one test every 11 months.

Figure 9 MCED bill only applies to Medicare enrollees aged 65 to 67, source: Congress

In addition, Medicare would then only adopt the MCED test if CMS determines that adoption is appropriate.[77] In our opinion, that 'appropriateness' decision will hinge on clinical data—likely from GRAIL's REACH study, assuming CMS accepts stage shift as valid. That data won't be available until at least September 2030.[78]

Even if all shortcuts succeed, GRAIL might only begin selling a curtailed version of its test by 2031—restricted to a narrow slice of its target market. **A simple heuristic shows that, despite FDA approval and the MCED Bill, the TAM shrinks to just 2.2%:**

1) Instead of 50 types of cancer, only 5 types of cancer are tested = 16.2% of the actual test[79]
2) Instead of all Medicare enrollees, only 65 to 67-year-olds are covered = 13.9% of total Medicare demographics.[80] [81]
3) 7.95% of the actual test multiplied by 13.9% of total Medicare demographics = **2.2% of the TAM**

The MCED bill allows GRAIL to access 2% of the projected TAM without demonstrating clinical utility. However, without a USPSTF recommendation, other governmental health programs and private payors will not be obligated to cover the test—for the rest of the population beyond the narrow Medicare subset targeted by the bill. As a result, **even with the passage of the MCED bill, Galleri faces a significant coverage gap, leaving 98% of its intended market inaccessible.**

Yet regardless of this, GRAIL has recently taken to touting partnerships with medical providers which streamline the Galleri ordering process for physicians.[82] [83] Most notably, its February announcement with Quest Diagnostics and a further release in May with athenahealth both sent GRAIL stock up by 15% or more on intra-day trading. In our opinion, this is primarily intended to pump GRAIL's share price.

2.3. Payors Deem Galleri *"Unproven"* and *"Not Medically Necessary."*

Irrespective of short-term boosts to investor sentiment, both announcements completely miss the point because: **it doesn't matter if physicians can order the Galleri test through a system.**

[77] https://www.congress.gov/bill/119th-congress/house-bill/842
[78] https://clinicaltrials.gov/study/NCT05673018
[79] According to CDC data, the 5-year prevalence rates for individual cancers are as follows: pancreas (0.021%), cervix (0.029%), head and neck (0.032%), liver/bile duct (0.019%), colon/rectum (0.144%) and ovary (0.039%). The combined prevalence of these five cancers is 0.14%, which represents approximately 16.2 % of the total 5-year cancer prevalence rate of 1.76% across all cancer types.
[80] https://data.cms.gov/summary-statistics-on-beneficiary-enrollment/medicare-and-medicaid-reports/medicare-monthly-enrollment/data
[81] The 13.9% are estimated from CMS data that counted around 15.9 million enrollees from age 65 to 69 (February 2025).
[82] https://grail.com/press-releases/grail-and-quest-diagnostics-provide-grails-galleri-multi-cancer-early-detection-mced-test-through-the-quest-diagnostics-test-ordering-system/
[83] https://investors.grail.com/news-releases/news-release-details/grail-and-athenahealth-team-offer-healthcare-providers

None of the five largest insurers (BUCAH) will reimburse it. A former GRAIL manager explained to us that if a test is categorized as "investigative and experimental", insurance companies will not pay for it:

> *"[…] A lot of payers out there issued what they call I&E, investigative and experimental medical policy decisions for Galleri when it was first launched. The reason for that is that lack of clinical utility data. You can go to United's website, look up Galleri, and you'll see investigative and experimental due to a lack of clinical utility data.* ***If you get that designation in their claim system, they're not paying for the test, no matter what****. […]"*

The former employee elaborated further, calling such a designation by any payer a "killer" for Galleri:

> *"[…]* ***Once you've got that designation,*** *the system when it sees an* ***81479*** *and then sees whatever identifier they have that makes it Galleri,* ***there'll be no fund sent to the patient for reimbursement. That's a killer from a testing standpoint. You want to avoid I&Es****. […]"*

The recently announced TRICARE coverage for the Galleri test falls into this "killer" category. According to GRAIL's own ordering guide (May 2025), **Galleri is assigned the widely scrutinized CPT code 81479**—often associated with tests lacking sufficient clinical evidence (see Figure 10 below).[84] TRICARE's coverage is not broad or guaranteed; rather, it is limited to case-by-case claims and is subject to stringent preconditions.[85] In other words, **this is not universal reimbursement—it is administrative ambiguity.**

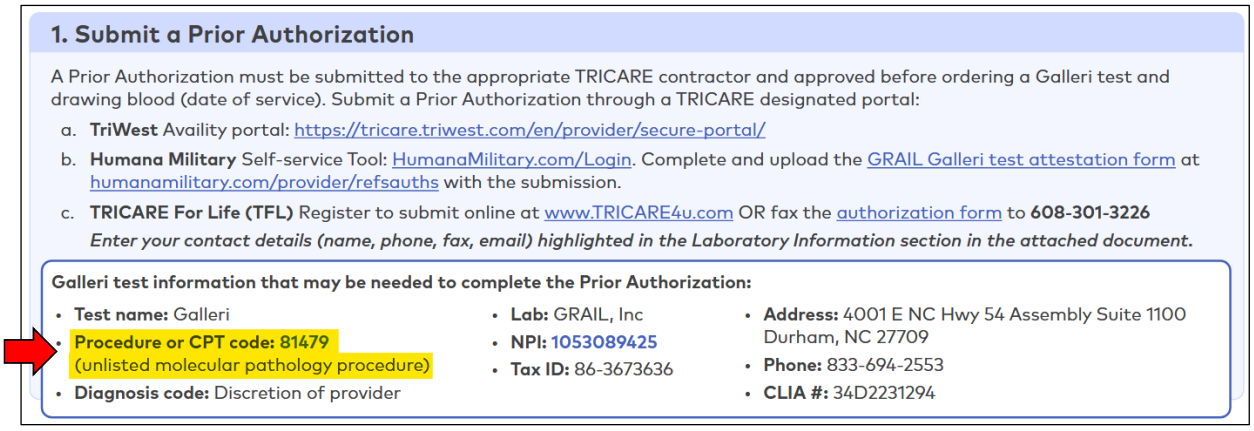


Figure 10 Galleri test is designated as 81479 for TRICARE coverage, source: GRAIL

Furthermore, we analyzed the medical policies published by Aetna, United Healthcare, Blue Cross, Humana, and Cigna in search of these "killer" terms—and, sure enough, in the most updated policy documents (see Figure 11), Aetna has stated in their medical policy (April 2025) that Galleri is listed under ***"liquid biopsy tests considered experimental, investigational, or unproven"*** while United Healthcare has recently classified the Galleri test as ***"not medically necessary"*** (May 2025); late last year (December 2024), Blue Cross simply described all MCED tests like Galleri as ***"Investigational; therefore, not covered",***

[84] https://assets.galleri.com/statics/Downloads/Tricare-Galleri-OrderingGuide20250528.pdf, pg. 2
[85] https://assets.galleri.com/statics/Downloads/Tricare-Galleri-OrderingGuide20250528.pdf, pg. 1

labeling it with the notorious 81479 code. [86] [87] [88] Humana has declined coverage for the Galleri test, while Cigna has designated it as ***"Not Covered"*** by specifically declining coverage for the cfDNA analysis that underlies the Galleri test.[89] [90]

Aetna - Clinical Policy for Tumor Markers (April 2025):

aetna™

Grail Galleri Test

Grail (Menlo Park, CA), a biotechnology company, developed the Galleri Test which utilizes a single blood test to check for more than 100,000 DNA regions and over a million specific DNA sites to screen for a signal shared by cancers that may otherwise go unnoticed. Specifically, the Galleri test looks for cell-free DNA and identifies whether the source is from healthy or cancer cells (Grail, 2023).

Currently, there is insufficient evidence in the peer-reviewed literature to support the sensitivity or specificity of this test.

United Healthcare - Medical Policy (May 2025):

Due to insufficient evidence of efficacy, all other molecular testing of solid tumors with GEP, multigene NGS panels, and/or CGP is unproven and not medically necessary, including but not limited to:

- NGS panels of > 50 genes unless otherwise specified
- Decipher® Bladder
- CancerTYPE ID®
- PancraGEN®, PancreaSeq®
- Oncotype DX® colon cancer assay, Colorectal Cancer DSA™, Genefx℠ Colon (also known as ColDx), OncoDefender™-CRC, ColoPrint®, ColonSentry®
- Blood based colorectal cancer screening tests (e.g., Signal-C, Guardant Shield)
- DecisionDx®-Melanoma, DiffDx™-Melanoma, DecisionDx®-SCC, DermTech PLA™, myPath® Melanoma
- Multi-cancer early detection/screening tests (e.g., Galleri®)
- TMPRSS2 fusion gene, ExoDX™ Prostate Test, MiPS (Mi Prostate Score Urine test), MyProstateScore (MPS

Figure 11 Aetna and United Healthcare medical policy, source: Aetna, UHC

One former sales manager told us that payors won't pay for it as it hinges on clinical utility data, meaning clinical evidence of mortality reduction:

> *"[…] They're going to review it, so they don't have to pay for it if they don't like it. Right now, given the database, they don't like it, same as the FDA, same as USPSTF.* ***They all have the same clinical hurdle that we got to address, and that's clinical utility data.*** *[…]"*

[86] https://www.uhcprovider.com/content/dam/provider/docs/public/policies/comm-medical-drug/molecular-oncology-testing-for-cancer.pdf, pg. 3
[87] https://www.aetna.com/cpb/medical/data/300_399/0352.html
[88] https://www.capbluecross.com/wps/wcm/connect/prod_nws.capblue.com29556/482b71ad-7d90-4862-9fac-60096683f1bb/medical-policy-2.387.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE.Z18_4G00HA41L8PI50ALUD09N53000-482b71ad-7d90-4862-9fac-60096683f1bb-oMBR6Ta
[89] https://assets.humana.com/is/content/humana/Liquid_Biopsypdf, pg. 5
[90] https://static.cigna.com/assets/chcp/pdf/coveragePolicies/medical/mm_0520_coveragepositioncriteria_tumor_profiling.pdf, pg. 27

No payer is covering GRAIL's Galleri test for the same reason it won't get recommended by the USPSTF or covered by CMS: Galleri will always lack data to prove clinical utility.

Ultimately, even if a curtailed version of the Galleri test obtains FDA approval, it is unlikely to secure a USPSTF recommendation or insurance coverage, as GRAIL lacks the critical mortality reduction data needed to overcome these regulatory and reimbursement hurdles.

Against this backdrop, we believe GRAIL's recent announcements—particularly those promoting streamlined ordering through partnerships like the one with Athenahealth—serve more to manage investor perception than to reflect meaningful clinical or regulatory progress. The fact that this press release was issued just 24 hours before a widely missed earnings report further reinforces this view.[91] [92] In our opinion, **GRAIL appears increasingly focused on market optics rather than on solving its underlying scientific and regulatory challenges.**

2.4. GRAIL Is Comparing Apples to Oranges, Misleading Investors About Its PPV

We weren't surprised that GRAIL recently touted that **the PPV from the NHS- was *"substantially higher"* than in PATHFINDER (43.1%)**—without disclosing the actual number.[93] In our opinion, this appears to be a distraction from disappointing quarterly results. **If the PPV was genuinely impressive, GRAIL would've published the figure**. We think the absence raises further concerns that the reported figure may result from selective analysis or subgroup slicing within the NHS-Galleri dataset.

This is not without precedent. **The last time GRAIL promoted a high PPV figure** from the NHS-Galleri program, it was **via the SYMPLIFY study—prominently featured during the company's 2024 Capital Markets Day.[94]** The headline 75.5% figure was derived from a cohort with a then-undisclosed, and unusually high, cancer prevalence of 6.7%, compared to the baseline prevalence rate of 1.76%.[95] [96] **Not long after, the associated journal published a correction that *"several values corresponding to the accuracy of the multi-cancer early detection tests have been updated"***—suggesting initial overstatement or methodological revision.[97] Notably, GRAIL has since removed the SYMPLIFY study from its clinical trials website.[98]

At a recent Jeffries conference, GRAIL and its CEO highlighted on a slide that *"The positive predictive value for Galleri in the population -- in the study population was 43%, which is an order of magnitude higher than leading single cancer screening tests."* [99] [100]

In our opinion, **GRAIL is repeating materially misleading claims about its PPV in comparison to existing screening methods.** In several investor presentations (see Figure 12 as an example), the company contrasts the 43.1% PPV reported in its PATHFINDER study with much lower figures from established

[91] https://investors.grail.com/news-releases/news-release-details/grail-reports-first-quarter-2025-financial-results
[92] https://grail.com/press-releases/grail-and-athenahealth-team-up-to-offer-healthcare-providers-streamlined-ordering-of-grails-galleri-multi-cancer-early-detection-mced-test/
[93] https://pmc.ncbi.nlm.nih.gov/articles/PMC11027492/
[94] https://investors.grail.com/static-files/084931e1-fc15-4d44-a2b9-9aac1887c2f6, pg. 54
[95][95] https://gis.cdc.gov/Cancer/USCS/#/NationalPrevalence/
[96] https://pubmed.ncbi.nlm.nih.gov/37352875/
[97] https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(24)00377-2/fulltext
[98] https://grail.com/clinical-studies/
[99] https://investors.grail.com/static-files/76c79035-cd52-45f0-afe8-123e11bb0dd3, pg. 9
[100] https://www.bamsec.com/transcripts/2ed587f3-5d87-4159-8f9a-75d9b8dcd48c

single-cancer screening tools: 1.2% for the fecal immunochemical test (FIT) for colorectal cancer, 3.8% for low-dose CT (LDCT) for lung cancer, and 4.4% for mammography in breast cancer.[101] [102]

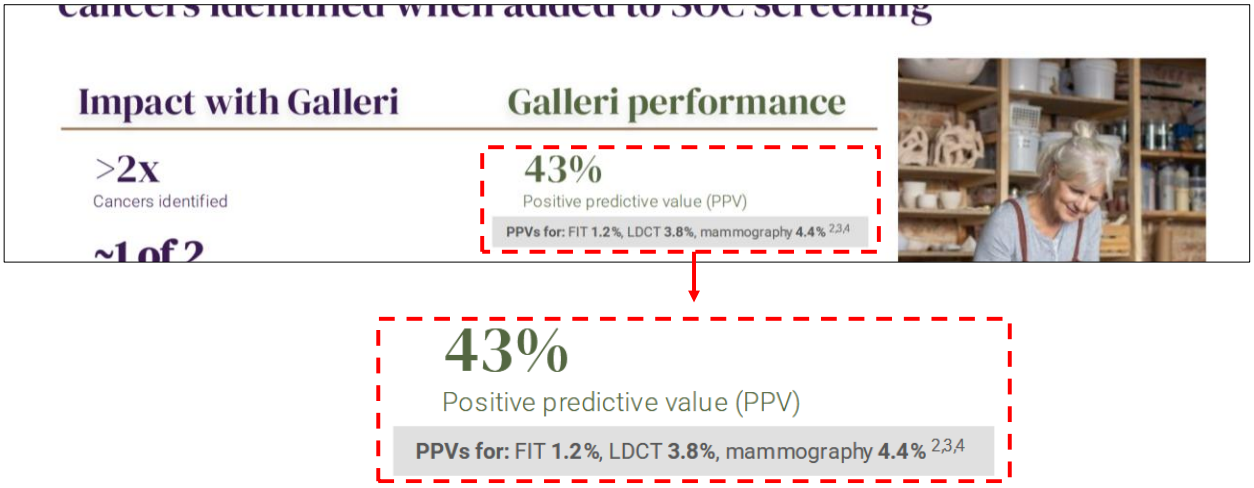


Figure 12 Extract from the recent presentation at a Jeffries conference, source: company filings

This comparison—presented without sufficient context—suggests a dramatic superiority of GRAIL's Galleri test, despite the fact that **the methodologies and populations differ substantially, rendering such comparisons equivalent to matching apples with oranges.**[103] [104] [105]

As discussed earlier, GRAIL has not disclosed the full clinical breakdown—true positives, false positives, true negatives, and false negatives—on a per-cancer basis from the PATHFINDER study, making it impossible for independent parties to verify these claims. However, when data from the case-controlled CCGA3 study is combined with cancer prevalence rates published by the CDC, the resulting **PPV per cancer is significantly lower**—one that aligns far more closely with existing screening methods or is even lower than the existing screening methods (see Figure 13 below).[106]

PPV, early stage	Galleri	FIT	LDCT	Mammography
Colon/Rectum	10.55%	1.20%		
Lung	5.17%		3.80%	
Breast	3.27%			4.40%

Figure 13 PPV for early-stage cancer compared between CCGA3 data and existing screening methods, source: NINGI Research, GRAIL, The New England Journal of Medicine, Radiology, Abdominal Radiology

We believe, given the case-control design of the CCGA3 study, the PPVs are inherently inflated, and **Galleri's performance is expected to decline further in real-world settings—undermining GRAIL's claim of superiority over existing screening methods.**

In our opinion, the routine promotion of the PATHFINDER PPV figure—absent transparent, cancer-specific performance data—represents a highly selective and misleading narrative for investors.

[101] https://investors.grail.com/static-files/084931e1-fc15-4d44-a2b9-9aac1887c2f6, pg. 42
[102] https://investors.grail.com/static-files/76c79035-cd52-45f0-afe8-123e11bb0dd3, pg. 9
[103] https://pmc.ncbi.nlm.nih.gov/articles/PMC4974132/pdf/nihms792670.pdf
[104] https://pmc.ncbi.nlm.nih.gov/articles/PMC3762603/pdf/nihms491916.pdf
[105] https://pmc.ncbi.nlm.nih.gov/articles/PMC5375631/pdf/radiol.2016161174.pdf
[106] PPV calculated using data from the CCGA3 study, CCGA3's overall specificity of 99.5%, and CDC's reported cancer prevalence rates (5-year duration).

This brings us to a deeper, structural concern: the question of leadership and internal governance. In our conversations with former employees and industry experts, a consistent narrative emerged—one where strategic missteps and unrealistic promises are not isolated miscalculations, but symptoms of a deeper dysfunction at the company.

3. Misguided and Mismanaged: GRAIL's Governance Failures

After in-depth discussions with experts and former employees, it has become clear to us that, as so often in similar cases, the problems start at the top of the organization—and are primarily born of a stubborn unwillingness to listen to the dedicated researchers, laboratory technicians, and scientific advisors who all got involved in the pursuit of GRAIL's noble quest. According to the former employees and industry experts we interviewed, there are issues with the GRAIL corporate culture so severe that they are driving away talent and demoralizing many of those who remain.

3.1. Drinking a GRAIL of Kool-Aid: No Room for Dissent, No Culture of Debate

One obvious reason for GRAIL's repeated missteps is that, even when the company specifically invites the scientific community to give it guidance, it refuses to take its advice. Such as that of **Donald Berry, professor at MD Anderson Cancer Center and former scientific advisor to GRAIL**, who told the company years ago that its clinical trial design was fundamentally flawed, but was rebuffed.[107] He went on to voice his criticism in the leading specialist publication *The Cancer Letter*, **saying that the company surrounded itself with *"people who had drunk the Kool-Aid."*** [108]

In the UK, meanwhile, the results of a recent investigation published in the BMJ revealed that **within the UK's National Screening Committee, high-level decision-makers were uneasy about the Galleri test** and the trial run with GRAIL, with the article obtaining e-mails hinting at *"behind closed doors"* agreements with political personalities.[109] Experts spoken to by the journal were unable to understand *"why a trial [was] being done on NHS patients of a test that showed so little promise in earlier trials."* [110]

It isn't just the British medical establishment that is concerned about GRAIL and its headline product. Back in 2021, an article in the **medical journal Diagnostics criticized the Galleri test, with high-profile researchers mounting a credible challenge of its empirical utility** by applying little to nothing more than a basic knowledge of algebra and biotechnology.[111] In 2022, an article in the New York Times spoke to users of MCED and demonstrated the possibility of unnecessary treatment stemming from the Galleri test's false positives.[112]

Yet GRAIL's reaction to such criticism is not to enter into dialogue and seek to understand it, but to immediately issue denials and rebuttals—indeed, in the case of the *New York Times*, on the same day the article was published.[113] [114] The *Diagnostics* article, meanwhile, was refuted in a piece written by GRAIL consultants, which concluded with various boilerplate statements.[115]

[107] https://www.nytimes.com/2022/06/10/health/cancer-blood-tests.html
[108] https://cancerletter.com/clinical/20241025_1/
[109] https://www.bmj.com/content/386/bmj.q1706
[110] https://www.bmj.com/content/386/bmj.q1706
[111] https://pmc.ncbi.nlm.nih.gov/articles/PMC8700281/
[112] https://www.nytimes.com/2022/06/10/health/cancer-blood-tests.html
[113] https://grail.com/stories/grail-statement-on-the-new-york-times-multi-cancer-early-detection-story/
[114] https://www.nytimes.com/2022/06/10/health/cancer-blood-tests.html
[115] https://pmc.ncbi.nlm.nih.gov/articles/PMC9141107/

3.2. Toxic Environment: GRAIL's Unholy Corporate Culture

In our opinion, the culture of denial seen in GRAIL's response to external criticism is mirrored internally. Multiple former employees independently described **the executive team as the company's most dysfunctional unit—consistently rated the worst in internal surveys,** then eventually shielded from those ratings altogether. Promotion practices were seen as arbitrary, transparency was scarce, and leadership, by several accounts, operated with open disregard for staff input. While the mission may have been noble, many who worked there told us the experience felt anything but.

Internally, it was an open secret that the leadership at GRAIL was falling short. One former executive stated bluntly:

> *"[…] **the executive team at GRAIL was rated the worst-performing unit within GRAIL for three straight years.** The feedback given was very specific. You're promoting people without interviewing. You're promoting people who've never managed people before. You're not telling anybody about the opening, so no one else can apply for it, and they continued."*

The former employee explained that, as he experienced GRAIL, ***"the executive leadership team would just do what it wanted. They didn't give a shit what people thought.*** *That was very clear to all of us."*

We also heard from former employees that, by the fourth year of GRAIL's internal survey, **the executive management stopped disclosing its internal survey ratings anymore**, with one former employee interpreting this decision clearly:

> *"[…] They didn't want to tell us how bad they did when they can't even admit to how bad their scores were. **But it was one of the worst cases of hubris ever, like: yeah, we don't really care, and you don't count.** That was just the attitude."*

Another former high-ranking manager described similar dysfunction at the leadership level:

> *"[…] I think that the executive team was not a well-functioning team at all. I think **decisions were made for reasons other than what's the best way to show this test works** and get it on the market. […]"*

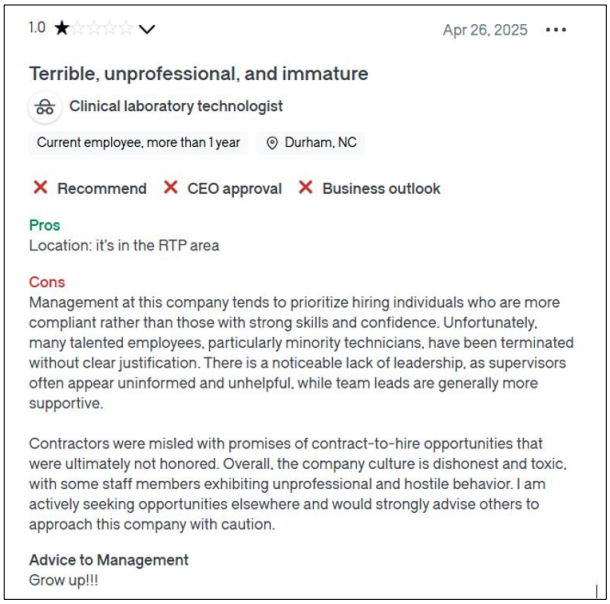
Other employees told us that the **corporate culture was challenging** to adapt to, and one former executive blatantly answered our question on GRAIL's corporate culture with:

> *"[…] I'll just say this, the culture is not a good culture. **It's a very terrible culture. You'll see that all over the internet. It's not a secret.** […]"*

On Glassdoor and Indeed, we consistently found specific criticism of the company's corporate culture—feedback that closely mirrored what we heard from former employees and industry insiders.[116]

[116] https://www.glassdoor.com/Overview/Working-at-GRAIL-EI_IE1280471.11,16.htm

Reviews described a leadership team insulated by Yes-Sayers, resistant to acting on employee feedback, and collectively lacking accountability (see Figure 14).[117]


1.0 ★ Apr 26, 2025

Terrible, unprofessional, and immature

Clinical laboratory technologist

Current employee, more than 1 year · Durham, NC

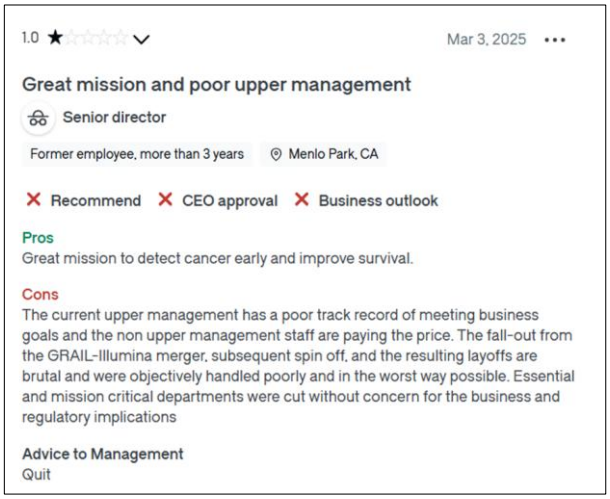
✕ Recommend ✕ CEO approval ✕ Business outlook

Pros
Location: it's in the RTP area

Cons
Management at this company tends to prioritize hiring individuals who are more compliant rather than those with strong skills and confidence. Unfortunately, many talented employees, particularly minority technicians, have been terminated without clear justification. There is a noticeable lack of leadership, as supervisors often appear uninformed and unhelpful, while team leads are generally more supportive.

Contractors were misled with promises of contract-to-hire opportunities that were ultimately not honored. Overall, the company culture is dishonest and toxic, with some staff members exhibiting unprofessional and hostile behavior. I am actively seeking opportunities elsewhere and would strongly advise others to approach this company with caution.

Advice to Management
Grow up!!!


1.0 ★ Mar 3, 2025

Great mission and poor upper management

Senior director

Former employee, more than 3 years · Menlo Park, CA

✕ Recommend ✕ CEO approval ✕ Business outlook

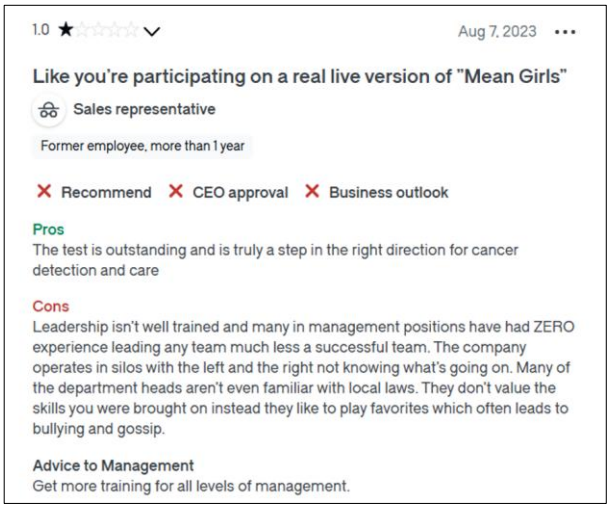
Pros
Great mission to detect cancer early and improve survival.

Cons
The current upper management has a poor track record of meeting business goals and the non upper management staff are paying the price. The fall-out from the GRAIL-Illumina merger, subsequent spin off, and the resulting layoffs are brutal and were objectively handled poorly and in the worst way possible. Essential and mission critical departments were cut without concern for the business and regulatory implications

Advice to Management
Quit

Figure 14 Glassdoor reviews criticized poor management, source: Glassdoor

One online **review likened GRAIL's culture to *"a real-live [sic] version of Mean Girls"*** (see Figure 15), while others compared it to a fraternity.


1.0 ★ Aug 7, 2023

Like you're participating on a real live version of "Mean Girls"

Sales representative

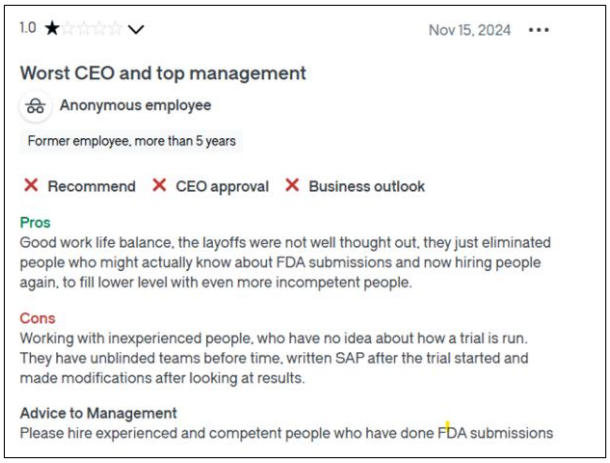
Former employee, more than 1 year

✕ Recommend ✕ CEO approval ✕ Business outlook

Pros
The test is outstanding and is truly a step in the right direction for cancer detection and care

Cons
Leadership isn't well trained and many in management positions have had ZERO experience leading any team much less a successful team. The company operates in silos with the left and the right not knowing what's going on. Many of the department heads aren't even familiar with local laws. They don't value the skills you were brought on instead they like to play favorites which often leads to bullying and gossip.

Advice to Management
Get more training for all levels of management.


1.0 ★ Nov 15, 2024

Worst CEO and top management

Anonymous employee

Former employee, more than 5 years

✕ Recommend ✕ CEO approval ✕ Business outlook

Pros
Good work life balance, the layoffs were not well thought out, they just eliminated people who might actually know about FDA submissions and now hiring people again, to fill lower level with even more incompetent people.

Cons
Working with inexperienced people, who have no idea about how a trial is run. They have unblinded teams before time, written SAP after the trial started and made modifications after looking at results.

Advice to Management
Please hire experienced and competent people who have done FDA submissions

Figure 15 Glassdoor reviews criticizing GRAIL's leadership and corporate culture, source: Glassdoor

In three different lawsuits, **former employees made allegations about a toxic, sexist, and racist work culture**.[118] [119] [120] One former employee alleged that GRAIL fostered *"[…] a fraternity house type of culture,"* with free alcohol available during office hours and **sales executives reportedly drinking beer during strategy meetings** for GRAIL's firefighter sales channel.[121] The same former staff member alleged that

[117] https://www.glassdoor.com/Overview/Working-at-GRAIL-EI_IE1280471.11,16.htm
[118] https://www.documentcloud.org/documents/23875688-tantum-complaint/
[119] https://www.documentcloud.org/documents/23875689-mansolilo-complaint/
[120] https://www.documentcloud.org/documents/23875687-cheung/
[121] https://www.documentcloud.org/documents/23875688-tantum-complaint/, pg. 18

GRAIL *"[…] had a culture of retaliation and failure to take disciplinary action against individuals who engaged in unlawful behavior."* [122] Another former employee *"was warned by previous women employees who had since left GRAIL that the company had a toxic culture."* [123]

Despite its noble goal, **GRAIL appears to have worn out a lot of employees**, **with one former director telling us** that most don't talk about their time at GRAIL: *"I don't know how many folks really want to talk because* ***most people who left, they've just moved on. It was a really toxic place to be."***

4. End of the Road: GRAIL Bleeding Cash.

In our opinion, GRAIL has pursued the wrong scientific path, and its leadership has consistently shown an unwillingness to listen to valid criticism—while fostering a toxic corporate culture in the process. With this in mind, it is perhaps no surprise that as both its regulatory prospects and its cash reserves dwindle, GRAIL appears to be pivoting towards questionable commercial practices while piling the pressure on an already strained workforce. While not surprising—in view of GRAIL's initial level of ambition and the noble character of its mission—we think this is deeply disappointing.

4.1. In Desperate Search of Sales

Lacking FDA approval, USPSTF recommendation, and insurance reimbursement as detailed above GRAIL has been forced into a direct-to-market approach to start generating revenue. Since 2021, it has been on the market nationwide as a laboratory-developed test (LDT).[124] [125] LDTs are diagnostic tests designed, manufactured, and used within a single laboratory facility operating under a CLIA (Clinical Laboratory Improvement Amendments) certificate and with FDA "enforcement discretion," meaning that the FDA has generally not enforced pre-market review requirements.[126]

A key limitation, however, is that many health insurers—including Medicare—do not reimburse LDTs for screening purposes (see Chapter 2.3). While a physician's prescription is still required, patients must typically take the initiative to book and pay for the test out of pocket.[127] **As a result, LDTs face inherently limited commercial potential.**

Yet this appears to have caught GRAIL's new leadership off guard following Illumina's re-acquisition of the company in 2021. According to a former sales manager, we spoke with:

> *"****[the new C-suite] wanted to turn it into a revenue-generating sales machine*** *immediately, and they didn't care to look at any of the work that's been done prior."*

Another former employee alleged that ***"salespersons and marketing teams were told to spend whatever it took*** *to build awareness in the market about the Galleri test."* [128] A lawsuit alleged, ***"GRAIL spent money effectively indiscriminately"****,* splurging millions of dollars on marketing, including PGA sponsorships,

[122] https://www.documentcloud.org/documents/23875688-tantum-complaint/, pg. 22
[123] https://www.documentcloud.org/documents/23875689-mansolilo-complaint/, pg. 6
[124] https://www.bamsec.com/transcripts/6ce6ed5e-fbd8-4577-8073-b9643b664aa3
[125] https://www.bamsec.com/transcripts/f9b48a4d-bc3d-432c-93ad-3abd0bcbf708
[126] https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests
[127] https://www.galleri.com/patient/faqs
[128] https://www.documentcloud.org/documents/23875688-tantum-complaint/, pg. 9

television ads, and even a custom-designed "Galleri Mobile Pod", a road-show testing facility that traveled around the country.[129]

In its pursuit of revenue, GRAIL pivoted toward enterprise sales and direct-to-consumer channels. The **enterprise segment** targeted large employers like Google and McKinsey, and life insurers such as John Hancock.[130] Companies did not pay upfront for enrollment capacity; instead, revenue depended on actual employee utilization—which, according to former employees, averaged just 30–40%. As a result, recognized revenue consistently lagged behind the initial deal size. Meanwhile, some life insurance partnerships unraveled in 2023 after GRAIL mistakenly sent false positive cancer notifications to policyholders.[131]

The **patient-initiated telemedicine (PIT) channel** was another attempt to generate revenue, allowing patients to order Galleri directly through an online portal, with oversight from third-party physicians and blood collection at Quest Diagnostics locations.[132] Driven primarily by aggressive advertising, the PIT channel leveraged emotionally charged messages emphasizing the idea that individuals can take control of their health.[133] Alarmingly, this appeal is often heightened by emotionally charged "what if?" messaging which plays on a sense of urgency and fear of missed detection.[134] [135] [136]

In the **concierge medicine sales channel,** the "what if?" is combined with affluent patients who can afford to pay out-of-pocket for the Galleri test. Concierge medical practices commonly cross-sell high-value services such as executive health screenings, cosmetic procedures, and anti-aging treatments. In our investigation, we found dozens of medical spas advertising the Galleri test, next to Botox and GLP-1 products.[137] [138] [139] [140] [141] Most of these clinics promote the Galleri with unproven claims or urgent calls like *"before it's too late."*[142] Some of these medical spas and longevity clinics appear less qualified, for example, they advertise the Galleri test as a screening method for brain tumors, which is of course not possible due to the blood-brain barrier.[143]

In conclusion, we believe that given the limited commercial potential of Galleri as an LDT, GRAIL and its intermediaries have leaned more on fear-based marketing than on evidence-based, factual communication.

4.2. High Ambitions, But Fundamentally Broken

Yet despite employing aggressive sales tactics, which are as ethically questionable as they are costly, **revenue has consistently lagged behind GRAIL's projections.** According to a publicly filed lawsuit, by January 2022 *"it became clear that GRAIL was nowhere near hitting anticipated sales forecasts. Sales were*

[129] https://www.documentcloud.org/documents/23875688-tantum-complaint/, pg. 9
[130] https://investors.grail.com/static-files/084931e1-fc15-4d44-a2b9-9aac1887c2f6, pg. 28
[131] https://www.ft.com/content/b91fc966-649e-4cd5-9e95-812987d27a51
[132] https://www.documentcloud.org/documents/23875688-tantum-complaint, pg. 5
[133] https://www.cancertherapyadvisor.com/news/misleading-social-media-posts-promote-mced-tests-other-medical-tests/
[134] https://www.instagram.com/reel/DGf8fpKz9pr/
[135] https://www.facebook.com/reel/1837636886995445
[136] https://www.youtube.com/watch?v=8DegtZhZm3A
[137] https://www.mymdspa.com/cancer-testing/
[138] https://www.theaestheticfirm.com/galleri-multi-cancer-early-detection-test
[139] https://neuronmedical.com/galleri-multi-cancer-early-detection-test/
[140] https://drvictoriafalcone.com/the-galleri-early-cancer-screening-test/
[141] https://www.instagram.com/p/DFqEfUjpkwG/
[142] https://hyperfitmd.com/services/galleri-cancer-test/
[143] https://www.mymdspa.com/cancer-testing/

not accelerating." [144] Revenue figures have remained persistently dismal, consistently failing to meet expectations—including the recent missed estimates in Q1 2025—and continue to hover at around only 10% of the forecasts presented to investors in 2020.[145] [146] [147]

These original projections, made by Illumina and GRAIL and described at the time as conservative, estimated revenue of $462 million for 2023 and $892 million for 2024 (see Figure 16).[148]

(*In millions*)	2021E	2022E	2023E	2024E	2025E
GRAIL Forecasts:					
GRAIL Total Revenue – Management Case A Estimate	$ 19	$ 119	$ 462	$ 892	$1,704
GRAIL Total Revenue – Management Case B Estimate	56	327	1,042	2,142	4,075
GRAIL Operating Profit (Loss) – Management Case A Estimate	(427)	(586)	(576)	(454)	(110)
GRAIL Operating Profit (Loss) – Management Case B Estimate	(436)	(589)	(427)	(37)	920
Unlevered Free Cash Flow:					
GRAIL Unlevered Free Cash Flow – Case A Estimate	(424)	(541)	(566)	(453)	(156)
GRAIL Unlevered Free Cash Flow – Case B Estimate	(433)	(541)	(431)	(87)	719

Figure 16 GRAIL's revenue projections by Illumina and GRAIL, source: company filings

The reality, however, has been even more disastrous: **GRAIL generated just $75 million and $108 million in Galleri sales in 2023 and 2024 respectively (see Figure 17).[149] That's 84% less than projected for 2023 and 87% less than projected for 2024.**

	Year Ended		
	December 31, 2024	December 31, 2023	January 1, 2023
Revenue:			
Screening revenue[(1)]	$ 108,627	$ 74,999	$ 39,817
Development services revenue	16,968	18,106	15,733
Total revenue	125,595	93,105	55,550
Total costs and operating expenses	2,314,753	1,608,487	5,498,440
Loss from operations	(2,189,158)	(1,515,382)	(5,442,890)

Figure 17 Extract from GRAIL's annual report, highlighting the company's significant underperformance, source: company filings

Back in 2020, GRAIL projected approximately $1.7 billion in revenue for 2025.[150] This now stands in stark contrast to its recently issued guidance, which implies just 20% to 30% revenue growth next year—suggesting net sales closer to $140 million.[151] That would be nearly 92% below the initial forecast. **In our**

[144] https://www.documentcloud.org/documents/23875688-tantum-complaint/, pg. 9
[145] https://www.documentcloud.org/documents/23875688-tantum-complaint/, pg. 7
[146] https://www.sec.gov/Archives/edgar/data/1699031/000169903125000041/gral-20241231.htm#i44201f55cf7f4f0e8efd0cb432c465a6_85
[147] https://www.sec.gov/Archives/edgar/data/1110803/000119312520302773/d801214ds4.htm, pg. 172
[148] https://www.sec.gov/Archives/edgar/data/1110803/000119312520302773/d801214ds4.htm, pg. 172
[149] https://www.sec.gov/Archives/edgar/data/1699031/000169903125000041/gral-20241231.htm, pg. 114
[150] https://www.bamsec.com/transcripts/80f0df2d-1970-4347-8020-e9b43eaa8c38
[151] https://investors.grail.com/static-files/76c79035-cd52-45f0-afe8-123e11bb0dd3, pg. 6

opinion, GRAIL has consistently overestimated its future revenue potential—just as it has overstated the clinical viability of the Galleri test.

Further, even sell-side analysts are increasingly pessimistic about GRAIL's future revenue growth. According to Koyfin, consensus estimates for 2025 and 2026 net sales (including development research revenue) come in at around $147 million and $173 million as against $1.7 billion and $3.9 billion estimates from GRAIL at the time.[152] [153]

It shouldn't come as a surprise that **GRAIL has been unprofitable since the start and that the company has lost money on each test it sells (see Figure 18 below).** And by 'lost money', we are not talking about accounting losses due to amortization of its research and development outlay, but real cash burn.

Unit costs, in USD	Q1 2025	FY2024	FY2023	FY2022	FY2021
Tests sold in reporting period	*37,000*	*137,000*	*94,000*	*49,000*	*11,000*
Revenue per test	789.46	796.26	804.80	812.59	859.45
COGS per test	1,367.43	1,534.77	2,025.39	3,388.35	5,013.45
Gross profit per test	**(577.97)**	**(738.52)**	**(1,220.60)**	**(2,575.76)**	**(4,154.00)**
R&D expense per test	1,449.32	2,490.68	3,823.43	6,726.04	41,837.45
Sales & Marketing expense per test	945.38	1,123.78	1,726.51	2,496.49	11,393.27
General & Administrative per test	1,218.22	1,561.80	2,132.70	3,553.22	58,022.73
Operating profit per test	**(4,190.89)**	**(5,914.77)**	**(8,903.23)**	**(15,351.51)**	**(115,407.45)**

Figure 18 Unit costs per Galleri test, source: company data

The Galleri test is listed at a price of $949, but as revealed in legal filings, the volume discount rate is approximately $650 per test.[154] Looking further into GRAIL's fundamentals reveals that the average selling price was $787 per test in 2025—slightly below the averages of $792 in 2024, $797 in 2023, and $798 in 2022 (see Figure 18). **The Galleri test remains deeply unprofitable across the board, as illustrated in Figure 18**. Since 2021, losses have narrowed, but our analysis of the financial statements indicates that recent improvements were primarily due to the termination of 30% of the workforce as of September 30, 2024.[155] This large-scale cost-cutting initiative reduced operating expenses by 26.9%, from $5,685 per test in Q3 2024 to $4,190 per test in Q1 2025 (see Figure 19 below).

Unit costs, in USD	3/31/2025	12/31/2024	9/30/2024	6/30/2024	3/31/2024
Tests sold per quarter	*37,000*	*40,000*	*32,600*	*35,200*	*29,200*
Revenue per test	789.46	788.78	778.34	800.09	806.13
COGS per test	1,367.43	1,609.15	1,516.66	1,399.46	1,616.23
Gross profit per test	**(577.97)**	**(820.38)**	**(738.31)**	**(599.38)**	**(810.10)**
Operating expenses per test	3,612.92	3,497.43	4,947.06	46,118.72	7,038.12
Operating profit per test	**(4,190.89)**	**(4,317.80)**	**(5,685.37)**	**(46,718.10)**	**(7,848.22)**

Figure 19 Units costs in the last few quarters, source: company data

Despite cost-cutting measures in Q3 2024, operating expenses resumed their upward trajectory in Q1 2025—rising from Q4 levels and underscoring the fundamental unsustainability of GRAIL's business model (see Figure 19).[156]

[152] https://app.koyfin.com/estimates/eac/2v-nqfDpH
[153] https://www.sec.gov/Archives/edgar/data/1110803/000119312520302773/d801214ds4.htm, pg. 172
[154] https://s3.documentcloud.org/documents/23875688/tantum-complaint.pdf
[155] https://www.reuters.com/business/healthcare-pharmaceuticals/grail-cut-jobs-planned-hires-2024-by-about-30-2024-08-13/
[156] https://investors.grail.com/news-releases/news-release-details/grail-reports-first-quarter-2025-financial-results

The fundamental issue remains: unit economics are deeply negative. Every core operating cost consistently exceeds revenue per Galleri test, and with no realistic path to raising prices, even full reimbursement would not offset the ongoing burden of R&D, marketing, and administrative expenses. **In our opinion, breakeven will never be attainable.**

4.3. All Burn, No Breakthrough: GRAIL's Cash in Limbo

Despite never making a dime selling the Galleri test, as of the end of Q1 2025, GRAIL had around $677 million in cash on its balance sheet. Mainly because, after its former owner Illumina had to divest, the company gave GRAIL a 'leaving present' of around one billion dollars to fund operations for the next 2.5 years.[157] So, GRAIL already burned through a lot of its divorce settlement, and without any positive cash flow has fired a third of its staff in late 2024 to slow down that cash burn.[158]

With around $763 million in cash at the end of 2024 and an expected cash burn for 2025 of around $320 million, this will result in less than $443 million to run the company in the years 2026, 2027, and 2028. Even at a **'conservative estimate' of $150 million of cash burned annually, GRAIL will still be short of millions of dollars.**

Regardless, sell-side analysts have been aggressively projecting exponential growth trajectories for GRAIL to rationalize valuation targets—despite models showing sustained negative free cash flow exceeding hundreds of millions through 2032.[159] As outlined, such forecasts rest on an improbable sequence of regulatory and commercial hurdles: FDA approval, full USPSTF recommendations, congressional passage of MCED bill, CMS reimbursement approval, private payer reimbursement agreements, and drastic cost-of-goods reductions—each representing independent execution risks which, collectively, render the financial projections highly speculative at best.

So the facts of the matter are quite simple: in the absence of something genuinely miraculous occurring, GRAIL will run out of money by around early 2028. In our opinion, **GRAIL's valuation should remain anchored to its projected cash reserves through 2025—approximately $14.28 per share**—until legit FDA clearance and USPSTF endorsement are achieved. Or not.

[157] https://www.fiercebiotech.com/medtech/illumina-parts-ways-grail-divestiture-complete
[158] https://www.reuters.com/business/healthcare-pharmaceuticals/grail-cut-jobs-planned-hires-2024-by-about-30-2024-08-13/
[159] Canaccord Equity (2025), Blazing a trail in the lucrative MCED market while managing cash burn; initiating at BUY and $32 PT, pg. 118

Conclusion

In our opinion, **GRAIL's commercial story has increasingly diverged from its scientific promise**. While the company entered the market with bold ambitions to redefine cancer screening, we believe its strategy has failed to account for the full scope of regulatory, reimbursement, and operational challenges that ultimately determine market access in U.S. healthcare.

At the heart of the problem is the **Galleri test's positioning as a screening tool without robust clinical evidence** of mortality reduction—an essential benchmark for guideline inclusion and broad insurance coverage. The test is currently offered as a **Lab Developed Test, but this pathway lacks reimbursement support** from both Medicare and private payors. Multiple insurers have classified the test as ***"investigational"*** **or** ***"not medically necessary,"*** **effectively cutting off payment channels.**

We believe GRAIL's future rests on a sequence of contingencies: **FDA approval → USPSTF recommendation → CMS reimbursement → private payor adoption.** Each step presents a significant hurdle; taken together, success is just improbable.

Critically, GRAIL's registrational studies—**PATHFINDER 2 and NHS-Galleri—are built around surrogate endpoints such as stage shift, rather than mortality reduction**. This presents a structural barrier to USPSTF recommendation and CMS reimbursement, as both require clinical utility demonstrated through survival benefit. According to GRAIL's CFO, no such mortality data will be pursued due to prohibitive time and cost. **Without mortality reduction data, the test cannot gain the regulatory traction needed for broad reimbursement—regardless of FDA approval.**

Meanwhile, **GRAIL continues to promote headline figures like a 43.1% PPV**, often in isolation and without cancer-specific breakdowns. These numbers, drawn from select populations and case-control studies, don't reflect real-world screening conditions. **When adjusted for cancer prevalence using CDC data, Galleri's cancer-specific PPVs align with—or fall below—those of established single-cancer screening tools.** Yet GRAIL continues to compare these inflated figures with lower benchmarks, a practice we view as materially misleading.

Compounding these scientific and commercial challenges is **a corporate culture that former employees have characterized as dysfunctional, opaque, and even toxic.** Multiple lawsuits and insider testimony paint a picture of executive-level hubris, strategic disarray, and a disregard for internal and external feedback. Even as GRAIL hemorrhages cash and misses revenue targets by wide margins, **management appears more focused on narrative control than substantive course correction.**

Looking ahead, investor enthusiasm appears tethered to speculative catalysts—most notably, the proposed MCED legislation. However, even under optimistic interpretations, **the MCED bill would enable only limited reimbursement for a narrow Medicare subset**, and only if CMS deems the test appropriate. We think that is a tenuous foundation for a company with high capital intensity and persistent regulatory risk.

In our opinion, **GRAIL's fair value should be anchored to its projected cash reserves—approximately $14.28 per share**—reflecting a business with no viable reimbursement path, eroding scientific credibility, and limited strategic runway.

For all information herein, we are short GRAIL, Inc. (NASDAQ: GRAL).

Appendix

Refresher: basic study designs

Case-controlled studies compare two groups: cases (with a condition) and controls (without). Being retrospective, this design examines past exposures to identify risk factors. Researchers select cases based on the outcome and choose controls from the same population. They compare exposure frequencies between groups. These studies are efficient for rare diseases or long-latency conditions, being quicker and less expensive than other types. However, they're prone to bias, especially recall bias. Case-control studies are valuable for generating hypotheses and identifying potential causal factors, despite limitations. They play a crucial role in epidemiological research, particularly when randomized controlled trials are impractical or unethical. GRAIL's CCGA is a case-controlled study.

Prospective cohort studies follow a defined group of people over several years to observe how certain exposures or interventions affect outcomes. Data is collected in real-time, establishing clear temporal relationships between testing and subsequent diagnosis, making it ideal for evaluating screening tests, such as cancer detection before symptoms appear. These studies control for confounding factors and reduce bias through randomization and blinding when possible. Key performance metrics like sensitivity, specificity, and predictive values can be directly calculated by comparing test results with a gold-standard diagnostic method. Additionally, cohort studies allow researchers to compare disease rates in tested versus untested populations over time. GRAIL's PATHFINDER study is a cohort study.

Refresher: performance metrics

- **Sensitivity** is the proportion of people with cancer (confirmed by a gold standard method) who receive a positive result in the MCD test. It indicates the ability of a test to correctly identify people with cancer. A high sensitivity means that the test detects most cases of cancer, while a low sensitivity means that it misses many cases.
- **Specificity** is the proportion of people without cancer who receive a negative result from the MCD test. It represents the ability of a test to correctly identify people who do not have cancer. A high specificity means that the test correctly identifies most healthy people as cancer-free.
- **Positive predictive value (PPV)** is the probability that a person with a positive test result actually has cancer. It answers this crucial question: "If my test is positive, what is the probability that I have cancer?" PPV is calculated as: True Positive ÷ (True Positive + False Positive). For MCD tests, this metric is particularly important as it determines how many people need to undergo potentially invasive follow-up testing.
- **Negative predictive value (NPV)** is the probability that a person with a negative test result does not actually have cancer. It answers this question: "If my test is negative, what is the probability that I don't have cancer?" The NPV is calculated as: True Negatives ÷ (True Negatives + False Negatives).

Refresher: prevalence rates

- **Prevalence rates**, which measure how common a disease is within a population, play a crucial role in cancer screening decisions. High prevalence increases a test's positive predictive value (PPV), making positive results more likely to reflect true disease and improving screening efficiency. In low-prevalence settings, even accurate tests may produce many false positives, leading to unnecessary procedures, anxiety, and higher costs. Organizations like the U.S. Preventive Services Task Force (USPSTF), the Centers for Medicare & Medicaid Services (CMS), and private payors consider cancer prevalence when evaluating coverage and recommendations for screening tests. Ultimately, prevalence informs whether the benefits of early detection outweigh the financial and medical costs of screening at the population level.