LIFE SCIENCE TOOLS AND DIAGNOSTICS

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Foundations of Discovery, Drugs & Dx: Liquid Biopsy Panel Takeaways

April 5, 2023

- **Bottom Line: At our Foundations of Discovery, Drugs and Dx conference last week, we hosted GH's (OP) co-CEO Helmy Eltoukhy, NTRA's (OP) CEO Steve Chapman, ILMN's (OP) CMO Phil Febbo, M.D., & EXAS (OP) CSO Jorge Garces.** Our discussion covered the path ahead for what is proving to be NGS's largest clinical opportunity – cancer Dx. Panelists agree that CGP is the most mature but still has room to grow from indication expansion, earlier lines of therapy, and multiple tests per patient. Growth in clinical evidence for MRD is expected to help sustain momentum, with NTRA leading. CRC screening should see more performance data throughout 2023. MCED will require the most lift given multiple hurdles and very early days still.
- **2023 a catalyst-rich year for CRC screening.** ECLIPSE staging performance is expected in 2023, and should add clarity to GH Shield's utility in early-stage colorectal (CRC) detection. Read-outs from EXAS' BLUE-C (stool and blood) and potentially another blood-based CRC trial (PREEMPT CRC) are expected in 2023 to early 2024. Based on panelists' comments, it's clear that liquid biopsy still has a place in the multi-modal CRC screening market, with colonoscopy and stool-based tests first in line.
- **A number of hurdles remain for the MCED market.** GH is pursuing an anchor indication strategy in multi-cancer early detection (MCED) with multiple specificity cutoffs vs GRAIL (ILMN) and EXAS pursuing core MCED assay with single specificity cutoff. Panelists agree MCED market development requires major evidence generation from massive registrational trials and Congressional authorization for an eventual NCD. Those making the major investments required to clear these hurdles expect a highly defensible position from new competition.
- **MRD test developers are investing in multiple trials across different indications to build strong clinical evidence.** Current assays have headroom for future improvements, but ultimately the body of clinical evidence is necessary for broader oncologist adoption, including guideline inclusion for community oncologists.
- **CGP adoption to benefit from more drug approvals and usage in treatment monitoring.** Panelists believe there is substantial runway ahead in other indications beyond NSCLC and a few other core indications. Today, many years since complete genomic profiling (CGP) first launched, the market is still working towards getting advanced cancer patients tested once, with likelihood that repeat testing will increase & adoption among oncologists continues to grow.
- **Continued inside...**

Reason for report:
PROPRIETARY INSIGHTS

S&P 500 Health Care Index: **1,553.83**

Companies Highlighted

EXAS, GH, ILMN, NTRA

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Our DNA, Our Future Panel: The Road Ahead for NGS, Oncology Dx and Screening

At our Foundations of Discovery, Drugs and Dx conference last week, we hosted a panel with executives from leading oncology diagnostics companies to discuss the path ahead for what is proving to be the largest clinical dx opportunity within cancer diagnostics and screening (in CRC and MCED). Our conversation featured GH's co-CEO Helmy Eltoukhy, NTRA's CEO Steve Chapman, ILMN's CMO Phil Febbo, M.D., and EXAS CSO Jorge Garces.

The panel covered each of the key oncology markets from comprehensive genomic profiling (CGP), minimal residual disease (MRD) to CRC screening, and multi-cancer early detection (MCED) tests. Today, CGP is the most mature market with most penetration in lung, but still has room to expand across indications and drive volume, with treatment monitoring becoming standard of care and as these tests move to first in line. MRD is seeing strong initial uptake in its $20B market as seen by Signatera (NTRA) ramp, and a robust cadence of clinical data that will be key to sustaining adoption both for tumor-informed and tumor-naïve assays.

CRC screening remains a key focus for investors still as we hope to see staging data from the ECLIPSE trial this year and as other trials read out, including EXAS BLUE-C and Freenome PREEMPT CRC. Finally, we saw that companies are taking differing approaches to MCED, but they are united in the need to generate substantial clinical evidence and pave a path for reimbursement. We also touched on recent news on the rollback of prior authorizations (PA), which could include certain genetic tests.

Key takeaways from our conversation include:

1. **ECLIPSE staging performance still expected in 2023, which should add clarity on Shield's utility in early-stage cancer detection.** 2023 is also expected to see CRC data from EXAS' BLUE-C (stool and blood) and potentially another blood-based CRC screening trial. ECLIPSE performance points to a multi-modal market with colonoscopy and stool-based tests first in line, but liquid still has a place in the market based on the feedback and has room for future performance improvements.

2. **GH is using CRC as a gateway indication for their integrated MCED assay given the proven reimbursement path. Conversely, GRAIL (ILMN) and EXAS are pursuing a multi-cancer indication approval.** MCED market development will require significant evidence generation from massive registrational trials and Congressional authorization for an eventual NCD. Those making the major investments required to clear these hurdles expect a highly defensible position from new entrants.

3. **Clinical evidence generation is key to establishing clinical utility and driving MRD adoption and reimbursement.** MRD test developers are investing in multiple

trials across different indications to demonstrate the survival benefit MRD can provide. Current assays have substantial headroom for future improvements, but ultimately the body of clinical evidence is necessary for broader adoption among oncologists including guideline inclusion.

4. **Complete genomic profiling (CGP), either with or without tissue, has gained meaningful penetration in non-small cell lung cancer (NSCLC), but growth ahead is likely to be driven by more drug approvals and earlier lines of therapies.** The market for CGP tissue and liquid still has significant room to grow beyond lung as CGP is broadly adopted in other tumor types and

5. **Rollback in some of the prior-authorizations by leading commercial payers was welcomed as it should help reduce friction and ease ordering for providers.** Panelists welcomed the news of potential rollback of prior-auth by a large commercial payer. Connecting EHR data to orders and getting your service in-network with payers can also address the same payer concerns as PA without the operational burden.

2023 Remains a Catalyst-rich Year for CRC Screening Trials with Staging Data for ECLIPSE, Pivotal Data for EXAS BLUE-C Cologuard 2.0 and Potential Freenome PREEMPT Trial Readout

Since GH's announcement of 83% CRC sensitivity, 13% advanced adenoma sensitivity at 90% specificity, questions remain on performance breakdown by stage, with a particular focus on stage I/II, which will drive the utility of the assay. Our conversations with an ex-FDA MEDACorp KOL suggests that, barring a surprise in stage-based data, ECLIPSE performance is sufficient for FDA approval, though the test will be seen primarily as a cancer *detection* test rather than prevention given the low AA performance (LINK). With Freenome's PREEMPT CRC screening liquid biopsy expected to also read out in liquid biopsy next, GH Co-CEO Eltoukhy was skeptical that any other liquid assay would deliver meaningfully higher results. Recall, Freenome (Private) is expected to read out data from their prospective and large 49k patients PREEMPT-CRC study in 2H23 to 2024.

Talking about assay improvement from current levels: Co-CEO Eltoukhy sees significant room for future improvements to the assay, but confirmed that the current assay will be launched commercially pending FDA approval, which is expected in 2024. EXAS CSO Garces noted that Shield itself is an improvement from Epi proColon test but also highlighted potential biological hurdles to blood assays, such as limited ctDNA shedding in certain tumors. EXAS is conducting an improvement of its own FDA-approved stool-based assay with Cologuard 2.0, with performance read-out of the BLUE-C trial expected in mid-2023 followed by liquid data in late 2023. Both EXAS and GH have been biobanking samples to help with further assay development. The ex-FDA KOL also indicated that a randomized or real-world study will always be necessary to get an upgraded product approved, as the model

cannot be trained and tested on the same samples ultimately – thus necessitating a new study whenever there is substantial assay improvement.

Liquid has a place in the CRC screening market: Liquid biopsy CRC screening is positioned to increase the number of screened patients and reduce barriers to compliance. Co-CEO Eltoukhy believes a blood option will be a frictionless alternative to existing tests and will ultimately boost compliance, particularly in underserved areas.

CSO Garces agreed that offering patients more options will drive screening rates higher. He pointed to the rapid uptake of Cologuard by 45-49-year-olds relative to patients over 50 as an indicator of different patient priorities when selecting the screening option. EXAS is positioning itself as a single source provider of a variety of oncology tests, including different screening modalities and tests in therapy selection, MRD, and risk stratification. Separately, our conversations with MEDACorp KOLs indicate that blood-based testing will likely be seen as second in line to colonoscopy and stool-based tests based on current performance.

Figure 1. CRC and AA Screening Performance by Test

Method	Sensitivity		Specificity	USPSTF?	NCCN?	Medicare?	Frequency
	CRC	AA					
Invasive							
Colonoscopy	**95%**	**95%**	**90%**	Y	Y	Y	Every 10 yrs
Stool							
FIT	**74%**	**24%**	**96%**	Y	Y	Y	Annual
Cologuard	**92%**	**42%**	**87%**	Y	Y	Y	Every 3 yrs
Blood							
Shield	**83%**	**13%**	**90%**	N	N	N	TBD

Source: Company Filings

Anchor Indication vs Single Multi-Cancer Assay Debate Continues, Reimbursement Path and Evidence Are Major Hurdles to Clear

GH is using CRC as a gateway to multi-cancer screening given the clear regulatory path and lower specificity required for single indications. We estimate CRC screening to be a $20B market within a larger $50B MCED TAM. GH is pursuing CRC as an anchor indication for an integrated MCED assay given the clear regulatory and reimbursement path. This “stacking of tumor types or indications” approach is different than what’s taken by GRAIL and EXAS with their single MCED assay that has all the tumor types in one assay. Lung is Shield’s next planned indication, and GH expects read-out of the 600 prospective patient NCIRE-LUNG study in late 2023 to mid-2024 and first endpoint read-out of the 10k Shield-Lung trial in 2025. Assuming a positive read-out, GH indicated that they could submit for FDA approval in 2026. Currently, lung screening reimbursement is limited to low dose CT scans for high-risk patients, but GH expects improvement from those levels. GH argues that assay design needs to account for the next step after a positive CRC has colonoscopy to end the

odyssey, but cancers like pancreatic cancer lack a clear next step. To account for this, Shield in its multi-cancer approach is using different specificity cutoffs for different tumor types to balance the tradeoff between sensitivity and specificity. For example, CRC specificity is 90% while other tumor types are likely be much higher (98%+).

Figure 2. GH MCED Data to Date

Company	GH			GH		GH			
Assay	Shield			Shield		Shield			
Event	AACR 2023			ASCO 2022		AACR 2022			
Date	Apr-23			Apr-22		May-22			
Trial Design	Retrospective Case Controlled Analytical Validation			Retrospective Case Controlled Analytical Validation		Retrospective Case Controlled Analytical Validation			
Indication	CRC	Lung	Other	CRC	Lung	CRC	Lung	Pancreas	Bladder
N Total	5,000	3,300	3,300	5,348	5,348	3,136	2,053	1,904	1,946
N Healthy	3,000	3,000	3,000	3,982	3,982	1,862	1,862	1,862	1,862
N Cancer	2,000	300	300	1,366	1,366	1,274	191	42	84
Specificity	90%	90%	98%	90% / 95% / 98%	90% / 95% / 98%	90%	90%	95%	95%
Sensitivity				93% / 86% / 72%	92% / 86% / 66%				
Stg I / II Sens*	93%	75%	66%	92%	90%	90%	87%	73%	52%
Stg III / IV Sens*				95%	93%				
TO Specificity	90%	90%	98%	98%	98%	98%	98%	98%	98%
TO Sensitivity	91%	85%	75%	99%	98%	99%	94%	88%	86%

Source: Company Publications

In contrast, GRAIL (ILMN) and EXAS are investing in massive trials for their core MCED assays with single specificity cutoff. Currently, just 5 cancer types have any type of recommended screening (CRC, lung, breast, cervical, and prostate). ILMN CMO Febbo believes MCED is a paradigm shift that will require large scale trials not to measure performance but also understand the work up that follows a positive test. GRAIL is investing in several trials, most notably the 140k patient trial with NHS and the 20k pivotal PATHFINDER 2 trial in the US. While NHS data can support FDA approval, US data is also required. CMO Febbo also argued that a tissue-of-origin (TOO) element is necessary to avoid sending all positive patients to PET-scan.

EXAS also expects to present additional validation data from ASCEND 2 before initiating SOAR, their FDA registration trial (80k+ individuals) for the MCED assay. CSO Garces noted the importance of multi-omics in the assay design, citing the doubling of cancers found in the Detect-A study with the inclusion of proteins and DNA mutation markers, with only 4% overlap between the two. This multi-omic approach contrasts with GRAIL's Galleri, and only uses methylation.

All the panelists involved with MCED agree that the scale of clinical evidence required defends them from new competition, particularly in a higher cost of capital market today. Even if new technology were to emerge, CMO Febbo noted that Oncotype Dx's and G360's market strength stems not just from the technology but also the substantial body of clinical evidence supporting their usage. Beyond the cost and trial barrier, the MCED market will need Congressional authorization for Health and Human Services (HHS) to issue a

national coverage determination (NCD) for MCED. CSO Garces noted that these challenges have brought competitors together to lobby for the changes needed to enable this opportunity. Bolstering the case for MCED, CMO Febbo argued that broad-based MCED could accomplish 50% of President Biden's Cancer Moonshot goal of reducing the cancer mortality rate by 50% in 25 years.

Figure 3. EXAS MCED Data to Date

Company	EXAS		EXAS	EXAS	
Assay	Mutli-Cancer Assay		Multi-Cancer Assay	CancerSEEK (Thrive)	
Event	ESMO 2022		AACR 2022	Detect-A	
Date	Sep-22		Apr-21	Jul-20	
Trial Design	Retrospective Case Controlled Validation		Retrospective Case Controlled Analytical Validation	Prospective Cohort Pilot Study	
Indication	MCED (4 Biomarker)	MCED (3 Biomarker)	MCED	MCED	MCED (w/ Imaging)**
N Total	1,132	1,132	437	10,006	10,006
N Healthy	566	566	257	9,910	9,910
N Cancer	566	566	180	96	96
PPV				19%	41%
Specificity	98.2%	98.8%	97.0%	98.9%	99.6%
Sensitivity	61.0%	53.4%	88.0%	27.1%	52.0%
Stg I	31%	20%			
Stg II	46%	38%			
Stg I / II	39%	39%	76%		
Stg III	68%	61%			
Stg IV	87%	85%			
Stg III / IV			92%		

Source: Company Publications

Figure 4. GRAIL (ILMN) MCED Data to Date

Company	ILMN / GRAIL		ILMN / GRAIL		ILMN / GRAIL	ILMN / GRAIL
Assay	Refined Galleri	Galleri	Refined Galleri	Galleri	Galleri	Galleri
Event	ESMO 2022		ASCO 2021		CCGA	AACR 2021
Date	Sep-22		Apr-21		Jun-21	Apr-21
Trial Design	Prospective Cohort		Prospective Case Controlled		Prospective Case Controlled Validation	Prospective Case Controlled Validation
Indication	MCED	MCED	MCED	MCED	MCED	MCED
N Total	6,621	6,621	6,629	6,629	4,077	982
N Healthy					1,254	464
N Cancer					2,823	518
PPV	43%	38%	40%	45%	44.4%	
NPV	99%	99%			99.4%	
Specificity	99.5%	99.1%			99.5%	99.5%
Sensitivity					51.5%	67.5%
Stg I / II					28%	42%
Stg III / IV					84%	89%
TO Precision	88%	97%	90%	85%	89%	92%

Source: Company Publications

Clinical Evidence Drives MRD Adoption; Remains the Most Meaningful Cancer Dx Market in the Near/Mid-Term

Companies involved in minimal residual disease (MRD) testing see clinical evidence as key to gaining adoption in the market. We estimate MRD is a $20B market that's roughly 6% penetrated today, with NTRA's Signatera currently leading (196k volume in 2022) followed by GH's Reveal and NEO's (OP) RaDaR – which is expected to make further inroads as a highly sensitive platform. NTRA CEO Chapman estimates CRC is about 10% penetrated, with about 30% of all oncologists having used Signatera. With 40 peer-reviewed publications and more trials ongoing, CEO Chapman argues that NTRA is starting to demonstrate the clinical utility of MRD. In our view, CIRCULATE is the most notable publication to date (LINK). The study demonstrated that MRD+ patients at 4 weeks post-surgery had a statistically significant benefit to 18-month disease free survival (18M-DFS) from adjuvant chemotherapy (ACT) while ACT provided MRD- (negative) patients no statistically significant benefit to 18M-DFS. Though the study was observational, it does support use of MRD to better stratify which patients will actually benefit from ACT. Ultimately, this trial was insufficient to support NCCN guideline inclusion, contrary to expectations (LINK). We expect that MRD will eventually gain inclusion as the stack of clinical evidence continues to build.

Co-CEO Eltoukhy believes tissue-naïve assays like Reveal face a high evidence bar, since a meaningful number of physicians intuitively believe tissue is needed for high sensitivity. GH is investing in multiple interventional studies that will read out performance in the major cancer types (lung, breast, and CRC) starting in late 2023/2024. Recall, Reveal grew 250% in 2022 despite significantly lower volumes vs Signatera, and management expects it to deliver low double-digit revenue in 2023.

EXAS CSO Garces highlighted the early validation of EXAS' assays that demonstrates how tissue-informed and -naïve assays can complement each other. EXAS plans to launch its tumor-informed assay as an LDT at the end of 2023. As physicians and payers get more comfortable with MRD in core cancer indications, CSO Garces believes there will be a shift towards pan-cancer reimbursement and guideline inclusion. Blue Cross Blue Shield CA pan-cancer coverage (effective 3/1/2023) in adjuvant, recurrence, and treatment monitoring is an early instance of this shift. NTRA's Signatera currently has MolDx coverage for immuno-oncology (IO), CRC, muscle-invasive bladder cancer (MIBC), and breast. Management estimates these indications total 3.4M tests per year.

MRD has substantial room ahead for performance improvements, but clinical utility remains key. The most notable near-term upgrade, in our view, is GH's incorporation of their new Smart Liquid Biopsy platform into Reveal in 2023 (LINK). Co-CEO Eltoukhy noted the upgrade will drive a 5x improvement to sensitivity, and GH had previously stated the assay will measure 1,000 biomarkers vs 50 today. He believes MRD is just at the beginning of the S-curve of what is possible and sees epigenomics as key for improving performance.

Likewise, NTRA CEO Chapman noted continued work on expanding tumor types and improving sensitivity, particularly in the recurrence setting where ctDNA is less prevalent, but noted the biological limits of detecting ctDNA. Despite the performance ramp ahead, GH Co-CEO Eltoukhy believes MRD will likely get added onto standard of care CT scans, but ILMN CMO Febbo felt more optimistic, arguing that radiology has hit its limit of detection. He sees MRD replacing screening while imaging will be necessary for locating the cancer. ILMN CMO Febbo also noted the distinction between analytical and clinical sensitivity and cautioned that assays shouldn't be so sensitive that it picks up irrelevant signals.

CGP Penetrated in Lung, but Some Cancer Patients Still Don't Get Testing. Drug Approvals and Treatment Monitoring Drive Future Growth

Complete genomic profiling (CGP), either with or without tissue, has meaningful penetration in advanced lung cancer patients, and growth ahead will be driven by more drug approvals and treatment monitoring opportunity. Recall, we estimate CGP is a $10B market with ~700k advanced cancer patients that we believe is 20% penetrated across liquid and tissue. Panelists believe there is substantial runway ahead in other indications that physicians perceive as less mutated. Even after many years since CGP first launched, the market is still working towards getting advanced cancer patients tested once. Long term, Drs. Eltoukhy and Febbo see large opportunity in using CGP for treatment monitoring to help doctors switch therapies when cancers develop resistance. Continued drug approvals for new targets are key to growing the actionability of the panels and gaining physician adoption.

ILMN's TruSight Oncology 500, which is expected to deliver ~$100M in 2023, also accelerates adoption by offering distributed kit solution for hospitals looking to enable internal CGP testing. CMO Febbo believes that as innovations like ctDNA get more established, they begin to shift from centralized to decentralized testing. He sees early signs of this trend in CGP with reference labs like DGX (NR) and LH (NR) ramping the test. While EXAS CSO Garces noted benefits from the centralized model in owning customer relationships and a greater economic share, ILMN CMO Febbo sees decentralization as key to reaching underserved areas. CGP is well reimbursed by CMS, and commercial payer adoption is growing, with UNH (OP, Mayo) announcing commercial coverage in Feb. for G360 CDx and other CDx-approved assays in FDA-approved indications.

Prior-Authorization Rollback Welcomed for Routine Care to Improve Reimbursement Rate

Panelists viewed prior authorization (PA) as sometimes appropriate, but welcomed its potential rollback in routine areas of care. On the morning of the panel (3/29), the *Wall Street Journal* published an article stating that multiple commercial payers were considering rolling back PAs for services with high approval rates, including some genetic tests (LINK). The article also mentioned commitments to automating the process to improve efficiency.

ILMN CMO Febbo explained that PA evolved from payer's need to understand the service they were paying for given the limited number of codes used by a fragmented diagnostics market. While NTRA CEO Chapman agrees that PAs can be valuable, he argues that they have become an operational burden for physicians, even in more routine care areas. He cited multiples cases when it may be difficult to obtain a PA in the filing window, which ultimately leads to less payment, even for covered test usage. GH Co-CEO Eltoukhy echoed the sentiment that PAs add meaningful friction to testing. In addition to the proposed changes, CMO Febbo sees that in-network status with payers and integration into electronic health record systems like Epic connects health data to the test order and reduces the need for PAs.

Disclosures Appendix

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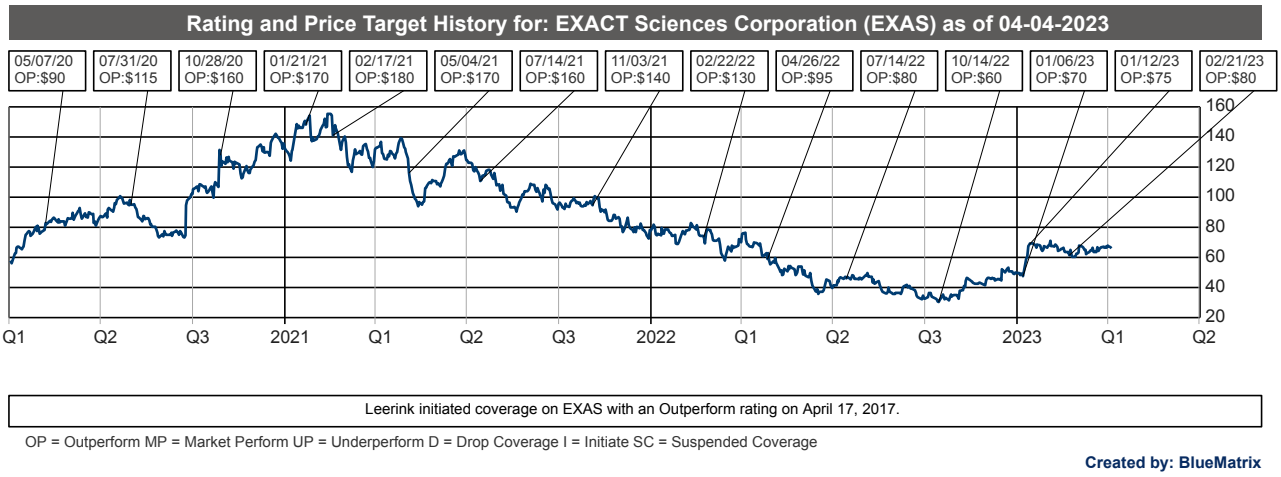
Analyst Certification

I, Puneet Souda, certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.



Valuation

Shares of EXAS currently trade at ~4.7x EV/Sales (consensus 2024E) – above the average of Dx peers of NVTA, CDNA, GH, CSTL, VCYT, NTRA, and ADPT at ~2.7x EV/Sales (2024E). We value EXAS by placing a ~6x EV/FY24E Sales multiple to yield a price target of $80. We believe that EXAS deserves a ~3x premium given ~40% of the population still remains unscreened in the US, and EXAS is only ~9% penetrated today in the $20B CRC screening market (SVB Securities estimate) of average risk individuals with multiple avenues for further penetration as the leading non-invasive test available in the market.

Risks to Valuation

The primary risks to our price target for EXAS include, but are not limited to: (1) worse-than-expected penetration with Cologuard; (2) better sensitivity from FIT tests being developed; (3) FDA regulations for its other LDT tests right now, including its lung and pancreatic tests; (4) reduction in reimbursement rates given political factors; (5) facility audits or Form 483 citations, which would halt Cologuard testing temporarily; and (6) reversal of positive decision from PAS study.

There is a possibility that Cologuard does not reach its serviceable market target despite growing adoption (9% penetration at 2022 year-end), as easier-to-use modalities (including blood-based assays) could attempt to gain penetration in this multi-modal market.

FIT tests or other competitors could develop enhanced sensitivity to compete with Cologuard. There are many generic FIT and FOBT tests that compete with Cologuard serving as non-invasive CRC screeners. If a generic

alternative to Cologuard were developed with a greater sensitivity, we believe there would be risks to the downside given that Cologuard pricing is about 20x that of a generic test. The difference in price that people are willing to pay is likely to decline as the gap between Cologuard and its competitors narrows. Currently, there are also blood-based tests such as Epi ProColon, Applied Proteomics (Not Rated), and Volition Rx (Not Rated) that look to compete in the non-invasive CRC screening market as well. However, current studies show that Cologuard is currently the best non-invasive option for CRC screening based on sensitivity and specificity.

FDA and regulations remain a risk for EXAS. Regulatory concerns from FDA decisions have an impact on EXAS's other tests. EXAS is still in the early stages of developing its lung, pancreatic and esophageal cancer diagnostic tests and could be impacted by the FDA. FDA regulations could impact development of products and the timing for the commercialization and clinical trials of certain tests. Increased regulations by the FDA will require additional SG&A expenses by EXAS to satisfy compliance. Increases in costs could also affect the ability to market its products for branding and public health education of the products.

Decrease in reimbursement would present a downside risk to our estimates. Currently, the reimbursement rate for Cologuard is well established at $500 with Medicare and commercial payers. Much of EXAS's revenues is based on reimbursement rates from Medicare. That impacts the number of tests administered and adoption rates of existing and new tests. Cologuard's revenue ramp would be severely impacted if its reimbursement rates fell. The recent political risks involving new Medicare policies that could potentially impact the reimbursement rate would have a significant effect on not only Cologuard, but other tests as well.

Profitability could be delayed further. EXAS has also partnered with the Mayo Foundation since 2009. In January 2016, EXAS entered into an agreement with Mayo where it will pay Mayo a low-single-digit royalty on net sales of products that have the Mayo name, including Cologuard, to 2033. We expect the royalty expenses to be categorized under COGS. In addition, EXAS paid Mayo installments of $1M in cash in 2017, 2018, and 2019. Newer studies and/or additional royalties could delay profitability longer than the current expectation of 2023.

EXAS's recently proposed acquisitions of Thrive Earlier Detection and Base Genomics create an additional closing and integration risk for the company. We expect the acquisitions are contributing to current market prices, significantly leveraging the company to the success of liquid biopsy cancer screening.

Valuation

We believe Guardant Health should trade to $50, our 12-month PT, based on DCF analysis. The PT also implies 8x EV/Sales (2024E), which is ahead of Dx peers group trading at ~3x. We have higher expectations for Reveal (MRD) and SHIELD (CRC Screening) in outer years beyond G360 and OMNI to drive our DCF with a WACC of 8.8%, a beta of 1.1, and long-term growth rate of 4.0%. Recall, we are likely to see upside from Guardant REVEAL growth in the cancer recurrence monitoring and MRD market longer term, beyond commercial G360, and higher reimbursement for all tests as both FDA approval and guideline inclusions follow.

Risks to Valuation

The primary risks to our price target for GH include, but are not limited to:

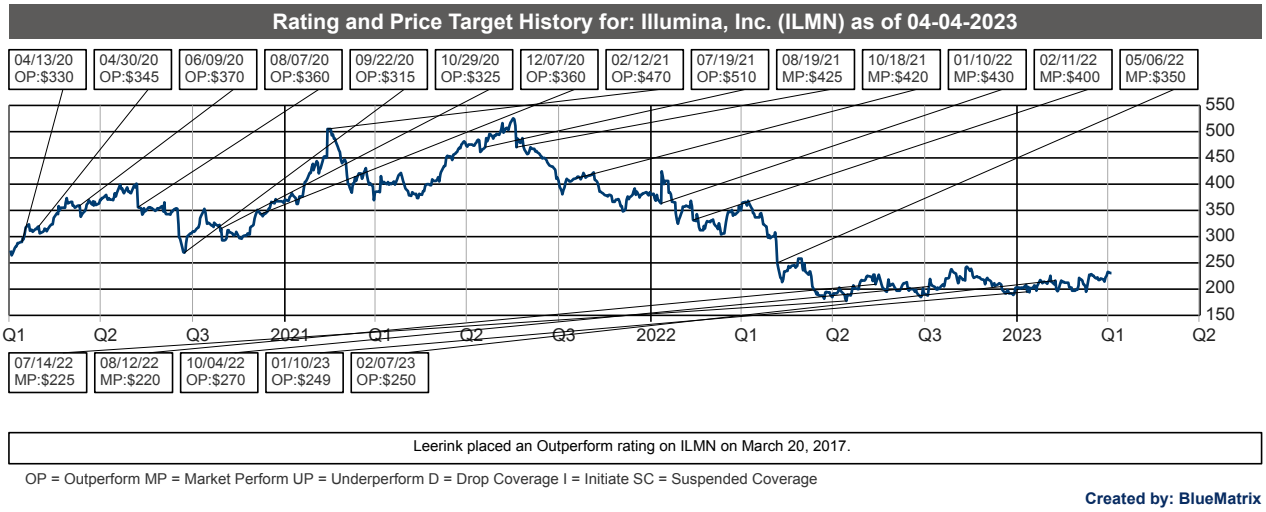
1. **Reimbursement dynamics could pressure ASP.** Decrease in reimbursement would present a downside risk to our estimates. Currently, the reimbursement rate for G360 has held roughly constant at $5,000, which is relatively high for the industry. Any dramatic changes in reimbursement of tests could impact profitability and outlook for the company.

2. **FDA regulations could impact a number of products offered by the company.** Change in regulatory landscape could impact the outlook for the company dramatically if FDA decides to regulate LDT (Laboratory Developed Tests), as is proposed by the VALID Act. FDA regulations could impact development of products and the timing for the commercialization and clinical trials of certain tests. Increased regulations by the FDA will require additional SG&A expenses by GH to satisfy compliance. Increases in costs could also affect the ability to market its products for branding and public health education of the products.

3. **Growing competition in MRD and liquid CGP.** An increasing number of companies are entering the MRD and liquid CGP space, potentially limiting GH's ability to command a price premium, particularly in more established markets like CGP. GH may also have to increase S&M spend to get physicians to order GH products over competitors.

4. **Regulatory uncertainty surrounding MCED go to market strategy.** GH is using a novel "anchor indication" strategy for MCED, where GH will add LDT indications over time to an FDA-approved CRC screening assay. Given early days in the regulatory landscape for MCED, this strategy could go fall short of requirements to get reimbursements for its MCED test, which would likely impact adoption of GH's assay.

5. **Delay in reaching positive cash flow could require additional financing**. It is possible that GH may need additional financing given expected negative net income in the near term, if its expected positive cash flow comes later than expected. If the company needs another round of financing for existing debt, this could lead to additional interest expense. Increased net debt on the balance sheet could also lead to increased capital costs.



Valuation

ILMN shares currently trade at a ~48.4x P/E on consensus 2024E EPS, a large premium to the average Life Science Tools (LST) group (TECH, TMO, A, ILMN, BRKR, PKI, DHR, WAT, QGEN, MTD) multiple of ~25x. We expect ILMN revenue to benefit from the launch of the NovaSeq X+, which we believe democratizes sequencing to include deep and broad applications like WGS and cancer screening. We see NovaSeq X+ utilization and installs exceeding NovaSeq X as sequencing intensive applications become more routine. Given the recent EC ruling, we believe ILMN is likely to explore divestiture options for GRAIL, taking away the current dilution to operating profit. To value ILMN, we use a DCF analysis with a WACC of 9.2%, long-term growth rate of 4.0% and a beta of 1.1 and arrive at a price target of $250.

Risks to Valuation

We see the following possible risks to our ILMN valuation:

1. Lower-than-expected NovaSeq X+ utilization and installs. Elasticity of demand takes longer than expected to catalyze new use-cases/applications and users on the research or clinical side. Installed base and utilization is slower to ramp to levels reached by the NovaSeq 6000. This can result in a negative revenue impact from lower cost per Gb outpacing volumes.

2. Loss of market leadership from competing high and mid throughout platforms. ILMN currently faces a number of emerging high throughput sequencing competitors including Ultima, PacBio, and MGI and mid throughput competitors such as Element. Sustained market share loss to competitors can negatively impact ILMN's outlook.

3. ILMN continues to appeal the European Commission's ruling regarding the divestiture of GRAIL into the foreseeable future. GRAIL is highly dilutive to ILMN's bottom line and creates significant cost disynergies for the company due to EC-stipulated measures to separate ILMN and GRAIL operations while antitrust challenges are ongoing. The timeline for an appeals process is uncertain and will continue to weigh on ILMN's stock and cost structure if management chooses to go down that path.

4. Macroeconomic challenges could increase caution in capital investment. Many companies, particularly smaller ones, are taking cost cutting measures to extend their cash runway or bolster their cash position ahead of a potential recession. This could affect demand for capital investments and consumable spending.

5. Decline in academic/research funding. A decline in research funding due to change in political leadership or periods of flat or declining allocations into research spending could severely curtail revenue growth.

OP = Outperform MP = Market Perform UP = Underperform D = Drop Coverage I = Initiate SC = Suspended Coverage

Created by: BlueMatrix

Valuation

NTRA is currently trading at ~3.7x consensus EV/2024E sales estimates. We assign a price target of $70 reflecting 5x EV/2023E sales on our revenue estimate of $1.27B. This EV/Sales 2024E multiple is a premium to SMID-cap Dx peers (NVTA, ADPT, NSTG, CSTL, EXAS, GH, VCYT, QDEL, and MYGN) average multiple of ~3.3x. We expect NTRA to continue to take share in the prenatal testing (NIPT) market, where it currently holds dominant ~50% market share. Longer term, we expect the larger oncology diagnostics market to remain as a driver of value for NTRA shares.

Risks to Valuation

Primary risks to our NTRA price target include:

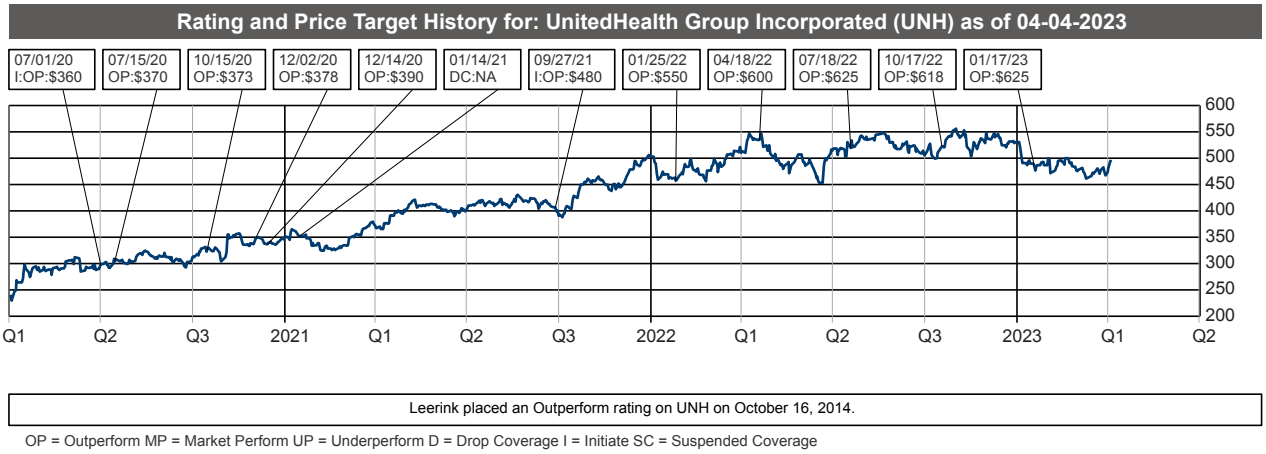
1. Natera is most levered to two products: Panorama and Horizon Carrier Screening tests, both situated in the reproductive health/testing market. Any disruption to the industry, which could come via government regulation, reimbursement decision, significant technological advancement by other companies and more, could change the growth trajectory of the industry, and Natera.

2. As a growth company, Natera continues to operate at a loss. These losses are expected to occur for the foreseeable future and may require the company to issue additional shares in order to raise capital, diluting current shareholder positions.

3. New test development uncertainty. As Natera is pursuing a relatively new technology in cell free DNA analysis, the ultimate shape of both the oncology and transplant rejection markets remains to be seen, offering risk in their long-term growth trajectory.

4. Natera operates in a competitive environment. The molecular diagnostics field is characterized by rapid technological changes, new product introductions, reimbursement challenges, competition, IP, price competition, aggressive marketing and commercialization tactics and evolving industry standards. Failure to keep up with changes in the industry could erode Natera's market share and significantly impact their long-term growth potential.

5. Commercial relationships. Natera has established commercial relationships with companies that could ultimately become competitors, especially ILMN. Natera has a contract with ILMN for sequencing and reagents; however, ILMN also owns competitor Verinata, which could potentially create a conflict of interest as the market grows. Furthermore, Natera has licensing agreements set up for OUS commercialization, including an agreement with BGI (Not Rated), which could ultimately become a competitive threat in China longer term.



Valuation

Our $625 price target is based on a 22x P/E multiple applied to our 2024 forecasts.This is largely in line with UNH's 1-year average forward valuation of 22.3x.

Risks to Valuation

- Higher-than-expected medical cost trends
- Regulatory or reimbursement changes from the state or federal governments
- A further decline in UNH's MA star ratings
- Future regulatory changes to the PBM model
- Increased competition in the commercial or government insurance space
- New regulation on the health plan side could disrupt how UHC conducts business
- UNH struggles to find suitable strategic M&A targets.

Distribution of Ratings/Investment Banking Services (IB) as of 12/31/22			IB Serv./Past 12 Mos.	
Rating	Count	Percent	Count	Percent
BUY [OP]	229	64.1	51	22.3
HOLD [MP]	113	31.7	8	7.1
SELL [UP]	15	4.2	1	6.7

Explanation of Ratings

Outperform (Buy): We expect this stock to outperform its benchmark over the next 12 months.

Market Perform (Hold/Neutral): We expect this stock to perform in line with its benchmark over the next 12 months.

Underperform (Sell): We expect this stock to underperform its benchmark over the next 12 months.

The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.

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In the past 12 months, SVB Securities LLC has received compensation for providing investment banking services to Natera, Inc.

SVB Securities LLC makes a market in EXACT Sciences Corporation, Guardant Health, Inc., Illumina, Inc., Natera, Inc. and UnitedHealth Group Incorporated.

SVB Securities LLC is willing to sell to, or buy from, clients the common stock of Quest Diagnostics, Inc. and LabCorp on a principal basis.

SVB Securities LLC has acted as a manager for a public offering of Natera, Inc. in the past 12 months.

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