



Transforming Disease Management



Fourth Quarter 2022
February 28, 2023

Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, which are subject to the “safe harbor” created by those sections. These forward-looking statements include, but are not limited to, statements concerning: generating between \$170-180 million in total revenue in 2023; estimated sizes of the total addressable markets of our current and future commercial and pipeline products within our dermatologic, gastrointestinal and mental health franchises, and our anticipated actions to further the growth of these franchises and products in 2023 and beyond, and any resulting financial or operational metrics or related expectations with respect to future performance; our ongoing studies generating data that further supports the clinical value of our tests and provider and payer adoption; and our expectations regarding catalysts of continued growth in 2023, including (i) publication of a collaborative NCI study showing higher melanoma specific survival for patients tested with DecisionDx-Melanoma, (ii) our new GI and MyPath commercial team expansion becoming substantially integrated into our sales and marketing efforts in Q2 2023, (iii) receiving a draft LCD for DecisionDx-SCC from Palmetto in the first half of 2023, (iv) the opening of our Pittsburgh lab in Q2 2023, and (v) further refinement of sales territories in our dermatologic, GI and mental health franchises. The words “can,” “estimates,” “expects” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions, or expectations disclosed in our forward-looking statements and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements that we make. These forward-looking statements involve risks and uncertainties that could cause our actual results to differ materially from those in the forward-looking statements, including, without limitation, the accuracy of our assumptions and expectations underlying our fiscal 2023 revenue target (including, without limitation, our assumptions or expectations regarding (i) continued reimbursement for our commercial tests at the current rates throughout 2023, (ii) our estimated total addressable markets for our products and product candidates and the related expenses, capital requirements and potential needs for additional financing, (iii) the anticipated cost, timing and success of our product candidates, and our plans to research, develop and commercialize new tests and (iv) our ability to successfully integrate new businesses, assets, products or technologies acquired through previously completed acquisitions); the effects of the COVID-19 pandemic on our business and our efforts to address its impact on our business; subsequent study or trial results and findings may contradict earlier study or trial results and findings or may not support the results discussed in this presentation, including with respect to the diagnostic and prognostic tests discussed in this presentation; actual application of our tests may not provide the aforementioned benefits to patients; and the risks set forth under the heading “Risk Factors” in our Annual Report on Form 10-K for the year ended December 31, 2022, and in our other filings with the SEC. The forward-looking statements are applicable only as of the date on which they are made, and we do not assume any obligation to update any forward-looking statements, except as may be required by law.

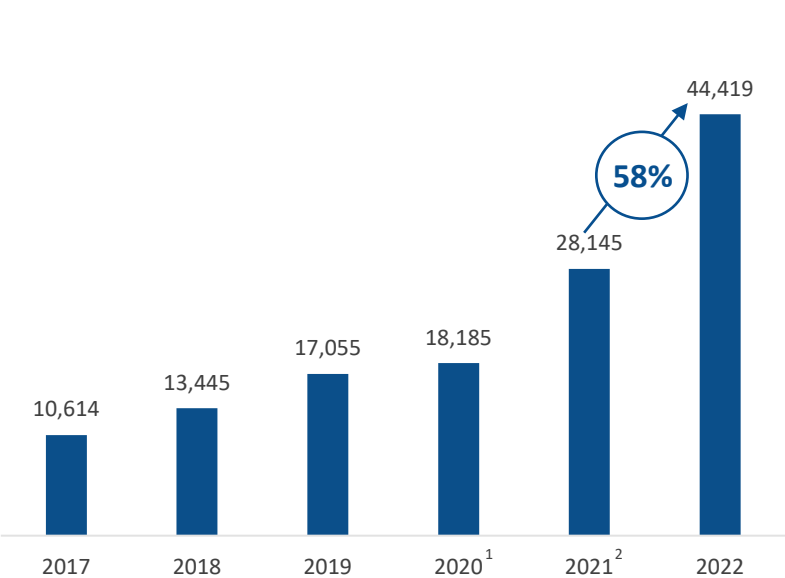
Strong Performance in 2022

Expecting approximately \$170 – 180 million in 2023 revenue

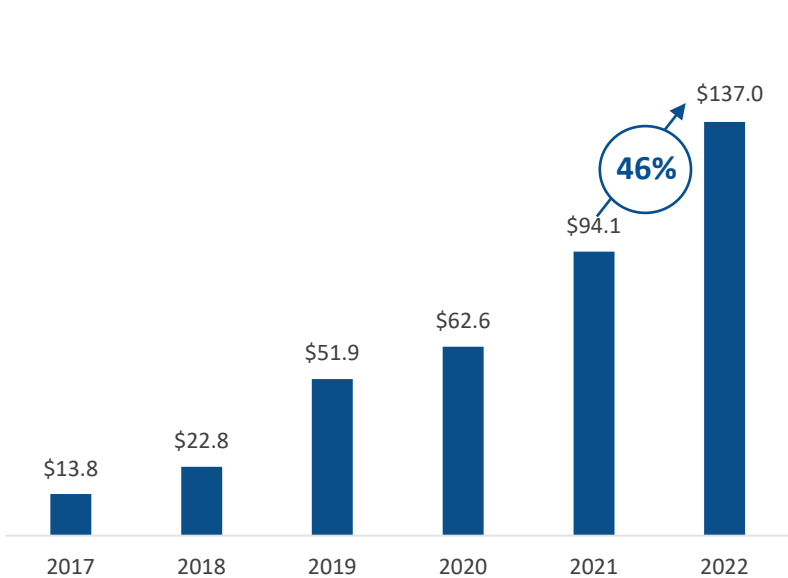
	2022	2021
Total test reports	44,419	28,145
Total Dermatology test reports	37,331	26,500
Revenues	\$137.0M	\$94.1M
Adj. Revenues ¹	\$139.0M	\$90.8M
Gross Margin	70.6%	81.1%
Adj. Gross Margin ¹	77.0%	82.6%
Net Loss	\$(67.1)M	\$(31.3)M
Adj. EBITDA ¹	\$(42.6)M	\$(14.9)M
Operating Cash Flow	\$(41.7)M	\$(19.0)M
Adj. Operating Cash Flow ¹	\$(41.7)M	\$(12.5)M
Cash, Cash Equivalents & Marketable Investment Securities	as of end of period \$259M²	\$330M

Consistent Execution of Growth Initiatives Supports Long-Term Growth

2017-2022 Total Test Report Volume



2017-2022 Revenue



¹Due to COVID-19, cutaneous melanoma diagnoses were down 20% for 2020; ²Cutaneous melanoma diagnoses were down 11% for 2021.

Key 2022 Accomplishments



Delivered strong year-over-year growth in revenue (met top end of guided range) and test report volume (total test reports delivered in 2022 were **44,419** up 58% over 2021)



Presented three-year financial targets and strategic guideposts at 2022 Investor Day



Developed expanded evidence supporting portfolio of innovative tests through the acceptance/publication of 14 peer-reviewed studies across all franchises



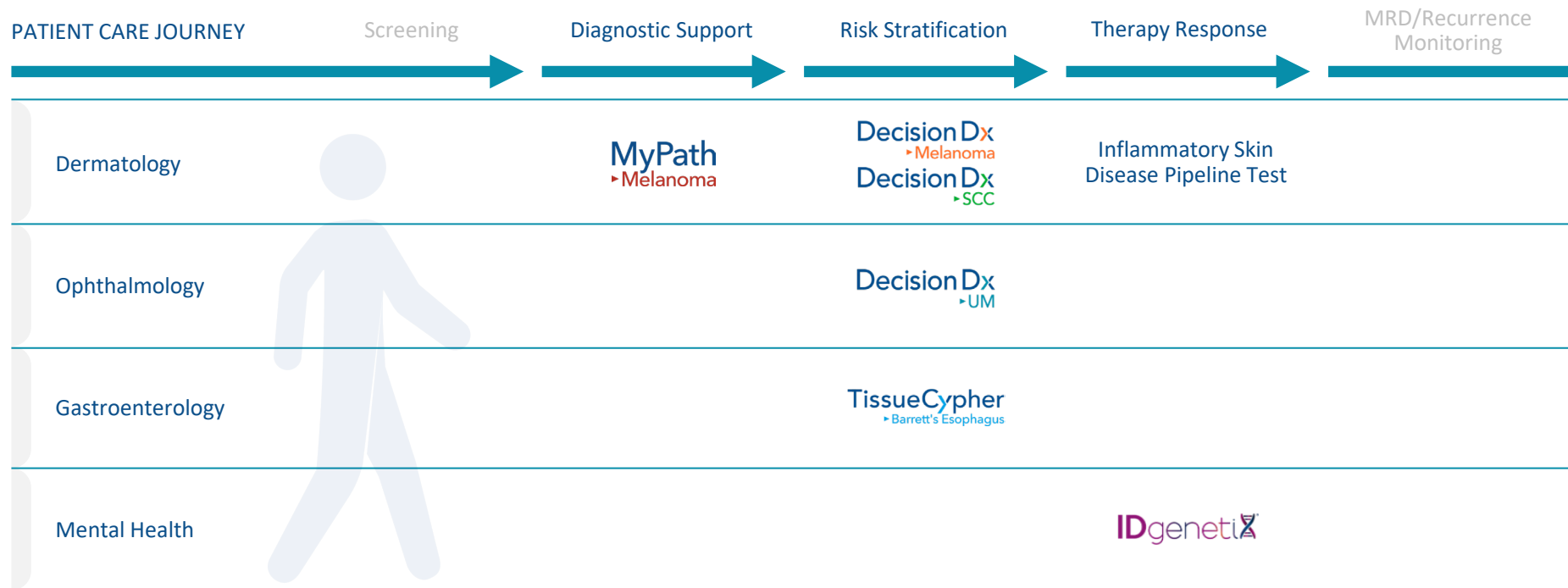
TissueCypher granted ADLT status by Medicare, recognizing the test for providing clinical diagnostic information that cannot be obtained from any other test or combination of tests



Transition of IDgenetix clinical services from San Diego lab and the folding of operations into our Phoenix location

Answering Clinical Questions to Guide Care Along the Patient Journey

Our focus is on diagnostic support, risk stratification and therapy response areas of the patient care continuum



Estimated ~\$8B U.S. Total Addressable Market¹ for Commercially Available Tests

	Dermatology		Gastroenterology	Mental Health
Cutaneous melanoma/ risk of metastasis, SLNB positivity risk	Cutaneous squamous cell carcinoma/risk of metastasis	Suspicious pigmented lesions/melanoma status	Barrett's esophagus/risk of progression to esophageal cancer	Mental health therapy response
~130K Patients classified as Stage I, II or III ²	~200K Patients w/high-risk features ²	~300K Patients w/ diagnostically ambiguous lesions	~415K Patients receiving upper GI endoscopies/year who meet the intended use criteria for TissueCypher ³	Based on indicated use of IDgenetix for patients diagnosed with depression, anxiety and other mental health conditions
~\$540M	~\$820M	~\$600M	~\$1B	~\$5B

Tests in pipeline add an additional estimated ~\$3.6B to our U.S. TAM
(\$1.9B for inflammatory skin disease pipeline test and ~\$1.7B for additional dermatology pipeline tests)

Significant Scientific Evidence Through Robust Clinical Research Program Across Our Testing Portfolio

13

Ongoing clinical research studies

231

Committed/contributing clinical research sites at year-end 2022

~11,200+

Patients¹ enrolled in studies at year-end 2022

~12,000+

Patients enrolled in studies over lifetime of Castle²

Ongoing collaboration with NCI/SEER has allowed for analyses of 9,200+ patients clinically tested with DecisionDx-Melanoma³ and 2,900+ patients clinically tested with DecisionDx-UM⁴ to date

Data as of Dec. 31, 2022

¹One TissueCypher study involves patients and ~250 physicians; ²Number reflects studies that span Castle's dermatology, ophthalmology and gastroenterology portfolios; ³SEER cancer registries linked CM cases diagnosed from 2013-2018 to data for patients with stage I-III CM tested with the 31-GEP as of Dec. 31, 2022; includes patients in studies not yet published; ⁴SEER cancer registries linked UM cases diagnosed in 2018 for patients with primary uveal melanoma tested with the 15-GEP; includes patients in studies not yet published.

Well Positioned for Continued Growth with Expected 2023 Catalysts



Expected publication of collaborative NCI study showing higher melanoma specific survival for patients tested with DecisionDx-Melanoma



Expect new GI and MyPath commercial team expansion to reach optimal productivity in Q2 2023



Expect draft LCD for DecisionDx-SCC from Palmetto in 1H 2023

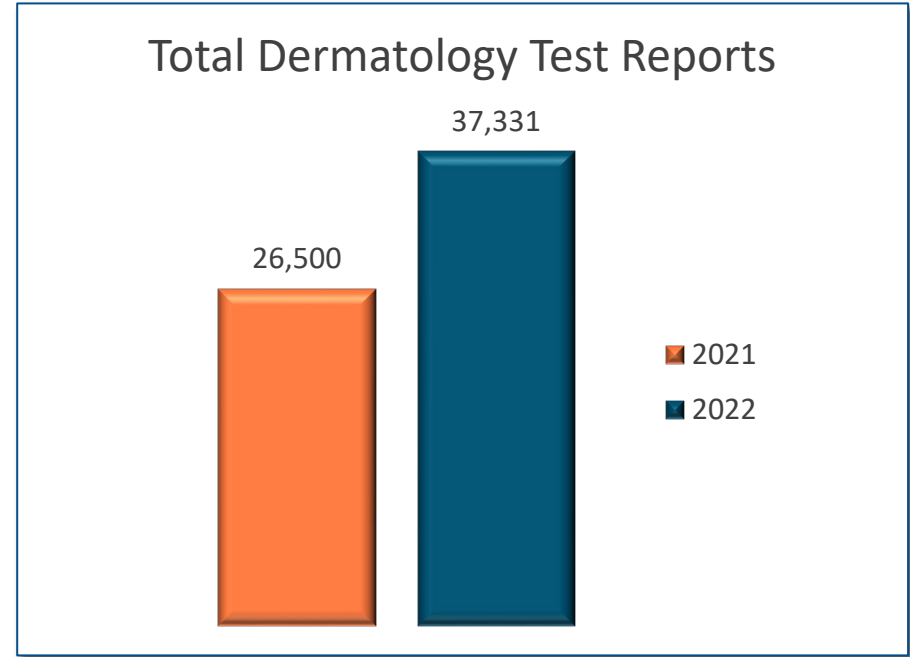
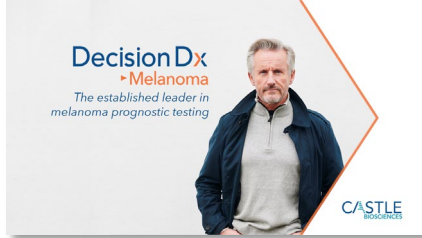


Pittsburgh lab opening in Q2 2023, bringing Castle's total laboratory operations space combined to 52,000 square feet



Further refinement of sales territories in our Derm, GI and Mental Health franchises

Strong Growth in Our Foundational Dermatology Business



Strong provider growth and continued adoption with ~2,312 new ordering clinicians and ~7,670 total ordering clinicians for our dermatologic tests for the year ended Dec. 31, 2022¹

DecisionDx-Melanoma Disease Specific Survival Outcomes Are Favorable Relative to Other Tests

Sentinel lymph node biopsy (SLNB)

- SLNB is a risk-stratification surgical procedure “test” in melanoma
- MSLT-1 found that SLNB had no impact on 10-year melanoma-specific survival¹

Tumor size	P-value	10-yr MSS
Thin (<1.2mm)	Not reported	Not impacted
Intermediate (1.2-3.5mm)	not significant (p=.18)	Not impacted
Thick (>3.5)	not significant (p=.56)	Not impacted

Breast Cancer Test

Breast Cancer Test ²	3-yr BCSS*
Breast Cancer Test	99.6%
Matched Untested	99.1%
Absolute Mortality Difference	0.50% (p<0.05)

BCSS mortality difference of **0.50% at 3 years** when comparing tested and untested populations

Decision Dx ► Melanoma

Decision Dx ► Melanoma	3-yr MSS ³
DecisionDx-Melanoma	97.7%
Matched Untested	96.6%
Absolute Mortality Difference	1.1% (p<0.05)

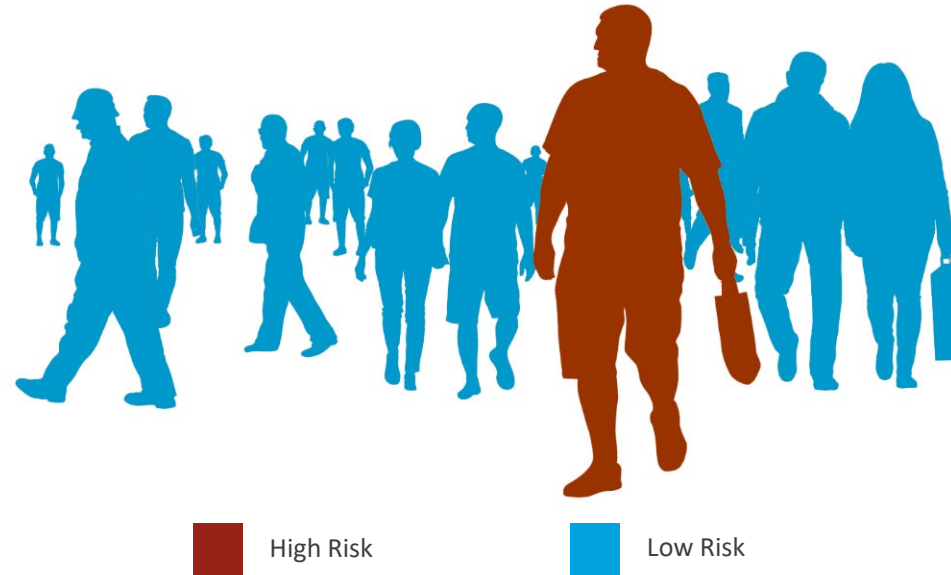
MSS mortality difference of **1.1% at 3 years** when comparing tested and untested populations

TissueCypher Is a Risk Stratification Tool for Patients with Barrett's Esophagus

Individualize 5-year risk of progression to HGD or EAC

- Indicated for NDBE, IND, and LGD
- High Risk score enables increased surveillance or early intervention to prevent cancer
- Low Risk score minimizes over treatment and supports extension of surveillance intervals to guideline recommendations

TissueCypher
► Barrett's Esophagus



IDgenetix: Precision Medicine Designed to Streamline Medication Selection for Mental Health

Next Generation PGx

- Eliminate trial and error prescribing
- 3 in 1 test:
 - Drug-gene interactions
 - Drug-drug interactions
 - Lifestyle factors

Unrivaled Efficacy

- 2x improved chance of medication response vs. control
- >2.5x improved chance of remission of depression symptoms vs. control

Easy to Use

- 10 mental health and pain conditions in one report
- <1 minute to collect DNA sample
- 3-5 days to receive test report
- Specialized sales and medical science liaison support

C/STLE
BIOSCIENCES

Thank you



Use Of Non-GAAP Financial Measures (Unaudited)

In this presentation, we use the metrics of Adjusted Revenues, Adjusted Gross Margin, Adjusted Operating Cash Flow and Adjusted EBITDA, which are non-GAAP financial measures and are not calculated in accordance with generally accepted accounting principles in the United States (GAAP). Adjusted Revenues and Adjusted Gross Margin reflect adjustments to net revenues to exclude changes in variable consideration related to test reports delivered in previous periods but not recorded as revenues until a subsequent period. Adjusted Gross Margin further excludes acquisition-related intangible asset amortization. Adjusted Operating Cash Flow excludes the effects of repayments to Medicare of COVID-19 government relief advancements to healthcare providers. Adjusted EBITDA excludes from net loss interest income, interest expense, income tax expense (benefit), depreciation and amortization expense, stock-based compensation expense, change in fair value of contingent consideration, and acquisition-related transaction costs.

We use Adjusted Revenues, Adjusted Gross Margin, Adjusted Operating Cash Flow and Adjusted EBITDA internally because we believe these metrics provide useful supplemental information in assessing our revenue and cash flow performance reported in accordance with GAAP, respectively. We believe that Adjusted Revenues, when used in conjunction with our test report volume information, facilitates investors' analysis of our current-period revenue performance and average selling price performance by excluding the effects of revenue adjustments related to test reports delivered in prior periods, since these adjustments may not be indicative of the current or future performance of our business. We believe that providing Adjusted Revenues may also help facilitate comparisons to our historical periods. Adjusted Gross Margin is calculated using Adjusted Revenues and therefore excludes the impact of revenue adjustments related to test reports delivered in prior periods, which we believe is useful to investors as described above. We further exclude acquisition-related intangible asset amortization in the calculation of Adjusted Gross Margin. We believe that excluding acquisition-related intangible asset amortization may facilitate gross margin comparisons to historical periods and may be useful in assessing current-period performance without regard to the historical accounting valuations of intangible assets, which are applicable only to tests we acquired rather than internally developed. We believe Adjusted Operating Cash Flow is also useful to investors as a supplement to GAAP measures in the assessment of our cash flow performance by removing the effects of COVID-19 government relief payment activity, which we believe are not indicative of our ongoing operations. We believe Adjusted EBITDA may enhance an evaluation of our operating performance because it excludes the impact of prior decisions made about capital investment, financing, investing and certain expenses we believe are not indicative of our ongoing performance, such as acquisition-related transaction costs. However, these non-GAAP financial measures may be different from non-GAAP financial measures used by other companies, even when the same or similarly titled terms are used to identify such measures, limiting their usefulness for comparative purposes.

Reconciliation of Non-GAAP Financial Measures (Unaudited)

The table below presents the reconciliation of adjusted revenues and adjusted gross margin, which are non-GAAP financial measures. See previous slide for further information regarding the Company's use of non-GAAP financial measures.

	Three Months Ended December 31,		Twelve Months Ended December 31,	
	2022	2021	2022	2021
<i>(in thousands)</i>				
Adjusted revenues				
Net revenues (GAAP)	\$ 38,338	\$ 25,039	\$137,039	\$ 94,085
Revenue associated with test reports delivered in prior periods	(806)	780	1,987	(3,324)
Adjusted revenues (Non-GAAP)	<u>\$ 37,532</u>	<u>\$ 25,819</u>	<u>\$139,026</u>	<u>\$ 90,761</u>
Adjusted gross margin				
Gross margin (GAAP) ¹	\$ 26,603	\$ 19,434	\$ 96,764	\$ 76,305
Amortization of acquired intangible assets	2,215	1,008	8,266	1,958
Revenue associated with test reports delivered in prior periods	(806)	780	1,987	(3,324)
Adjusted gross margin (Non-GAAP)	<u>\$ 28,012</u>	<u>\$ 21,222</u>	<u>\$107,017</u>	<u>\$ 74,939</u>
Gross margin percentage (GAAP) ²	69.4 %	77.6 %	70.6 %	81.1 %
Adjusted gross margin percentage (Non-GAAP) ³	74.6 %	82.2 %	77.0 %	82.6 %

1. Calculated as net revenues (GAAP) less the sum of cost of sales (exclusive of amortization of acquired intangible assets) and amortization of acquired intangible assets.
2. Calculated as gross margin (GAAP) divided by net revenues (GAAP).
3. Calculated as adjusted gross margin (Non-GAAP) divided by adjusted revenues (Non-GAAP).

Reconciliation of Non-GAAP Financial Measures (Unaudited)

The table below presents the reconciliation of adjusted operating cash flow, which is a non-GAAP financial measure. See slide 15 for further information regarding the Company's use of non-GAAP financial measures.

	<u>Three Months Ended</u> <u>December 31,</u>		<u>Twelve Months Ended</u> <u>December 31,</u>	
	<u>2022</u>	<u>2021</u>	<u>2022</u>	<u>2021</u>
<i>(in thousands)</i>				
Adjusted operating cash flow				
Net cash used in operating activities (GAAP)	\$ (6,000)	\$ (2,781)	\$ (41,655)	\$ (18,983)
Medicare advance payment ¹	—	2,999	—	8,350
HHS provider relief funds ²	—	—	—	(1,882)
Adjusted operating cash flow (Non-GAAP)	\$ (6,000)	\$ 218	\$ (41,655)	\$ (12,515)

1. We received an advance payment of \$8.3 million from the Centers for Medicare & Medicaid Service (CMS), for which recoupment has commenced in April 2021. We recorded the receipt of the payment as a liability on our balance sheet and, in accordance with GAAP, it was included in net cash provided by (used in) operating activities in the period received. We have excluded receipt of the advance payment from adjusted operating cash flow, but as claims were submitted for reimbursement and applied against this balance, we included the advance payment in adjusted operating cash flow to the extent that Medicare claims submitted for reimbursement were applied to the balance.
2. We received a one-time payment of \$1.9 million in relief funds automatically allocated to Medicare providers under the Coronavirus Aid, Relief and Economic Security Act (CARES Act) from the U.S. Department of Health and Human Services (HHS).

Reconciliation of Non-GAAP Financial Measures (Unaudited)

The table below presents the reconciliation of adjusted EBITDA, which is a non-GAAP financial measure. See slide 15 for further information regarding the Company's use of non-GAAP financial measures.

	Three Months Ended December 31,		Twelve Months Ended December 31,	
	2022	2021	2022	2021
<i>(in thousands)</i>				
Adjusted EBITDA				
Net loss	\$ (20,618)	\$ (6,430)	\$ (67,138)	\$ (31,292)
Interest income ⁽¹⁾	(2,275)	(17)	(3,968)	(68)
Interest expense	4	1	17	1
Income tax expense (benefit)	57	(8,725)	(1,766)	(8,720)
Depreciation and amortization expense	2,841	1,451	10,543	3,407
Stock-based compensation expense	9,923	6,851	36,321	21,740
Change in fair value of contingent consideration	(300)	—	(18,287)	—
Acquisition related transaction costs	—	—	1,711	—
Adjusted EBITDA (Non-GAAP)	<u>\$ (10,368)</u>	<u>\$ (6,869)</u>	<u>\$ (42,567)</u>	<u>\$ (14,932)</u>

1. Beginning in the fourth quarter of 2022, we began excluding interest income from the calculation of Adjusted EBITDA. Prior periods presented herein have been recast to conform to the current period presentation.

Appendix



Leadership Team Overview

MANAGEMENT TEAM

Derek Maetzold

Founder, Director, President and CEO



Frank Stokes

Chief Financial Officer



Toby Juvenal

Chief Commercial Officer



Stuart
Pharmaceuticals

Kristen Oelschlager, RN, CHC

Chief Operating Officer



Robert Cook, PhD

Senior Vice President, Research & Development



Northwestern



Matthew Goldberg, MD

Medical Director



Alice Izzo

Senior Vice President, Marketing



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Kimberlee Caple



Ellen Goldberg

CHORD Consulting