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Transforming Disease Management

First Quarter 2023
May 3, 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: our estimated U.S. total addressable market for our commercially available tests; our positioning for continued growth and expected 2023 catalysts; our ongoing studies generating data and their impact on driving adoption of our tests; and study observations and interpretations of study data, including conclusions about the benefits and impact of our tests on treatment decisions and patient outcomes. The words "anticipates," "can," "estimates," "expects," "target" 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: our estimates and assumptions underlying our estimated U.S. total addressable market for our commercially available tests; the effects of macroeconomic events and conditions, including inflation, banking crises, supply chain disruptions, the COVID-19 pandemic and geopolitical events, among others, on our business and our efforts to address their 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.

Financial Performance Summary Q1 2023

		Q1 2023	Q1 2022
Total test reports		**14,916**	8,627
Total Dermatology test reports		**10,974**	8,115
Revenues		**$42.0M**	$26.9M
Adj. Revenues[1]		**$43.4M**	$26.3M
Gross Margin		**70.5%**	71.7%
Adj. Gross Margin[1]		**76.5%**	77.4%
Net Loss		**$(29.2)M**	$(24.6)M
Adj. EBITDA[1]		**$(15.1)M**	$(11.4)M
Operating Cash Flow		**$(25.4)M**	$(21.4)M
Cash, Cash Equivalents & Marketable Investment Securities	as of end of period	**$232M[2]**	$309M

[1]See Non-GAAP reconciliations at the end of this presentation. [2]Year-over-year change in cash, cash equivalents and marketable securities includes the acquisition of AltheaDx in April 2022 and payout of annual bonuses in Q1 2023, among other uses.

Key Q1 2023 Accomplishments

With continued momentum from 2022, delivered a strong start to the year, with significant test report volume growth (a 73% increase over Q1 2022) and revenue growth (a 57% increase over Q1 2022)

Published prospective, multicenter study, called DECIDE,[1] showing DecisionDx-Melanoma test results influenced 85% of clinicians' decisions regarding the SLNB[2] surgical procedure and led to a significant reduction in SLNBs performed

National Society for Cutaneous Medicine endorses DecisionDx-Melanoma as offering more utility than other existing cutaneous melanoma GEP[3] assays or nomograms in consensus panel report

Received a 2023 Top Workplace USA award for an exceptional workplace culture; this is Castle's second year in a row to receive this national distinction

Shared performance data from a novel, multi-center, independent cohort demonstrating that DecisionDx-SCC can significantly improve metastatic risk predictions by complementing current staging systems (AJCC8[4] and BWH[5])

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[1]DECIDE=DecisionDx-Melanoma Impact on Sentinel Lymph Node Biopsy Decisions and Clinical Outcomes; [2]SLNB=sentinel lymph node biopsy; [3]GEP=gene expression profile; [4]AJCC8=American Joint Committee on Cancer 8th edition staging system; [5]BWH=Brigham and Women's Hospital staging system

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

Dermatology		MyPath Melanoma	DecisionDx Melanoma DecisionDx SCC	Inflammatory Skin Disease Pipeline Test
Ophthalmology			DecisionDx UM	
Gastroenterology			TissueCypher Barrett's Esophagus	
Mental Health				IDgenetix

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Estimated ~$8B U.S. Total Addressable Market[1] 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 ~$5.7B to our U.S. TAM

[1]U.S. TAM = Total addressable market based on estimated patient population assuming average reimbursement rate among all payors.[2]Annual U.S. incidence for Stage I, II or III melanoma estimated at 130,000; annual U.S. incidence for squamous cell carcinoma estimated at 1,000,000 with addressable market limited to carcinomas with one or more high risk features; annual U.S. incidence for suspicious pigmented lesion biopsies estimated at 2,000,000 with addressable market limited to the 15% with an indeterminant biopsy.[3]415,000 upper GI endoscopies/year with confirmed dx of BE (ND, IND, LGD, EXCLUDING HGD) x $2,513 = U.S. only TAM of ~$1 billion

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

18
Ongoing clinical research studies

323
Committed/contributing clinical research sites as of Q1 2023

~11,800+
Patients enrolled in studies as of Q1 2023

~18,000+
Patients enrolled in studies over lifetime of Castle[1]

Ongoing collaboration with NCI/SEER has allowed for analyses of 9,200+ patients clinically tested with DecisionDx-Melanoma[2] and 2,900+ patients clinically tested with DecisionDx-UM[3] to date

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Data as of March 31, 2023

[1]Number reflects studies that span Castle's dermatology, ophthalmology and gastroenterology portfolios, as well as tests that are currently or were in our development pipeline; [2]SEER 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; [3]SEER 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

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

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

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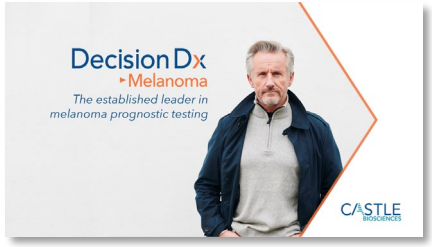
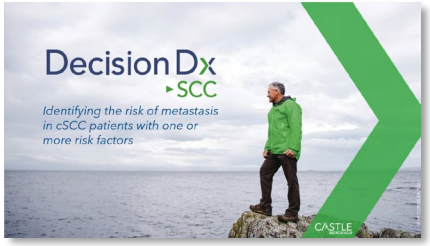
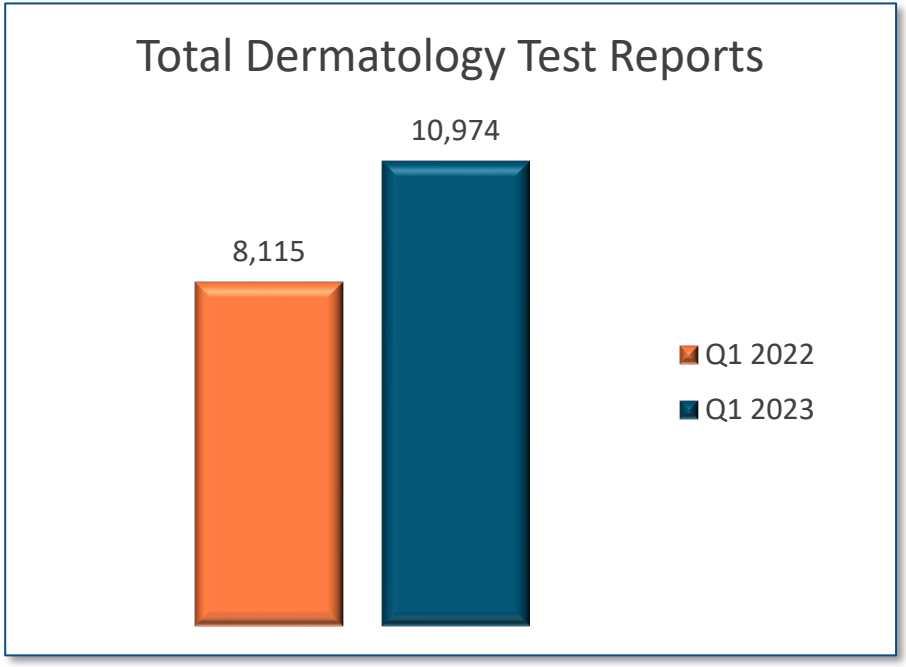
Strong Growth in Our Foundational Dermatology Business





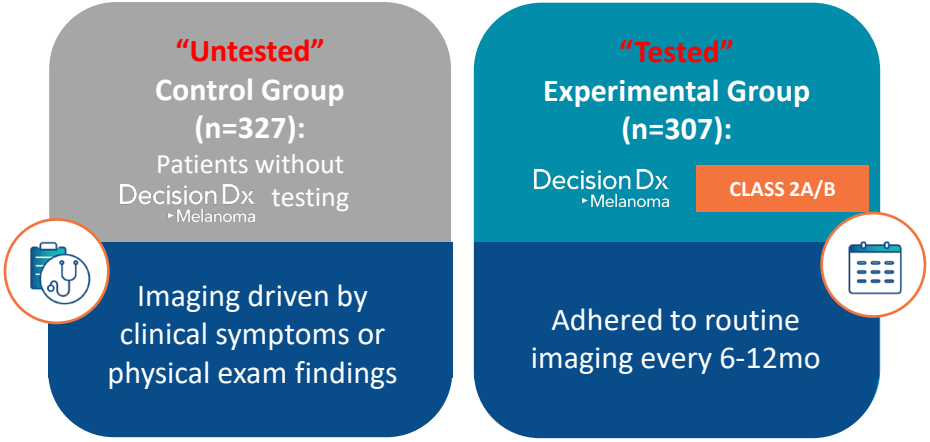


Strong provider growth and continued adoption with ~540 new ordering clinicians[1] and ~4,500 total ordering clinicians for our dermatologic tests for the quarter ending March 31, 2023

[1]New ordering clinician =clinician who ordered a Castle dermatologic test for the first time.

Direct Evidence Demonstrating Treatment Decisions Guided by DecisionDx-Melanoma Results Can Lead to Improved Patient Outcomes

Independent, multi-center study of SLN negative patients (n=634)



Key findings:

- DecisionDx-Melanoma test directed routine surveillance imaging in SLN-, high-risk patients detected melanoma recurrence **~10 months earlier** than those without routine imaging.
- Tumor burden at detection was significantly lower in patients tested compared to those not tested (27.6mm vs. 73.1mm)
- Patients tested had better overall survival than those not tested (76% vs. 50%, p-value= 0.027)

"Patients who received routine imaging after high-risk GEP test scores had an earlier recurrence diagnosis with lower tumor burden, leading to better clinical outcomes."

Dhillon et al. *Archives of Derm Research* 2023.

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 survival[1]

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

DecisionDx Melanoma

DecisionDx Melanoma	3-yr MSS[3]
DecisionDx-Melanoma	97.4%
Matched Untested	96.1%
Absolute Mortality Difference	**1.3% (p<0.05)**

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

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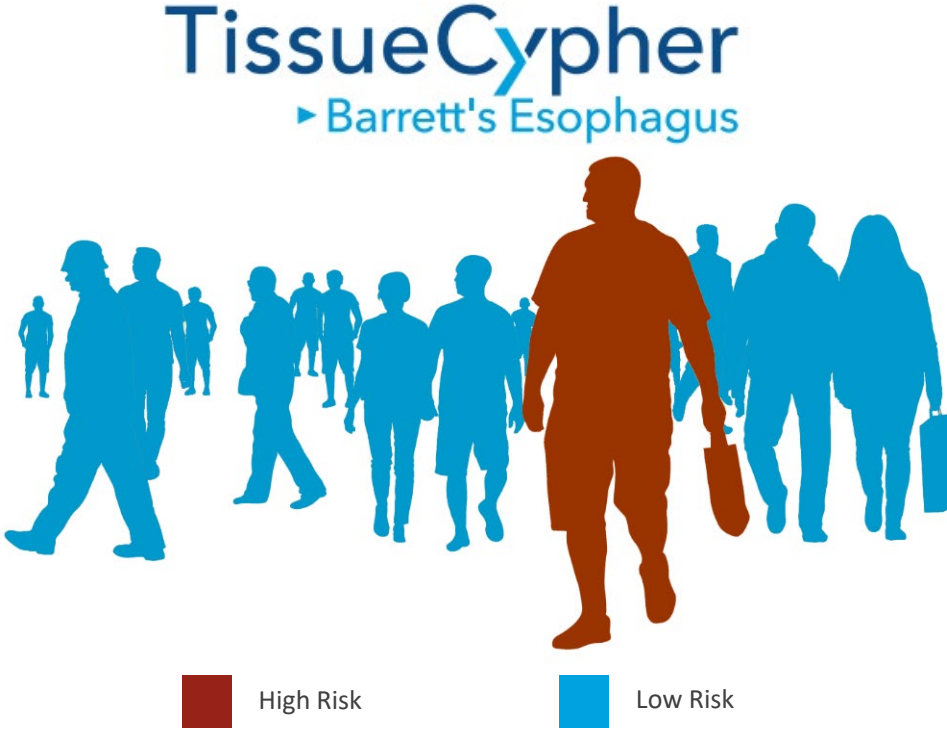
[1]Morton et al. *N Engl J Med* 2014; [2]Zhang et al. *Breast Cancer Res Treat.* 2020; [3] Manuscript accepted for publication at *JCO PO*. *https://apps.automeris.io/wpd/

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



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

Bradley et al. *J Psychiatr Res* 2018.

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Thank you

Use Of Non-GAAP Financial Measures (Unaudited)

In this presentation, we use the metrics of Adjusted Revenues, Adjusted Gross Margin 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. Adjusted Gross Margin further excludes acquisition-related intangible asset amortization. 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 and Adjusted EBITDA internally because we believe these metrics provide useful supplemental information in assessing our revenue and operating 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 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 March 31,	
	2023	2022
(in thousands)		
Adjusted revenues		
Net revenues (GAAP)	$ 42,037	$ 26,852
Revenue associated with test reports delivered in prior periods	1,336	(602)
Adjusted revenues (Non-GAAP)	$ 43,373	$ 26,250
Adjusted gross margin		
Gross margin (GAAP)[1]	$ 29,633	$ 19,260
Amortization of acquired intangible assets	2,222	1,648
Revenue associated with test reports delivered in prior periods	1,336	(602)
Adjusted gross margin (Non-GAAP)	$ 33,191	$ 20,306
Gross margin percentage (GAAP)[2]	70.5 %	71.7 %
Adjusted gross margin percentage (Non-GAAP)[3]	76.5 %	77.4 %

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).

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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 March 31,	
	2023	2022
(in thousands)		
Adjusted EBITDA		
Net loss	$ (29,204)	$ (24,623)
Interest income[1]	(2,336)	(30)
Interest expense	4	3
Income tax expense	14	134
Depreciation and amortization expense	2,892	2,151
Stock-based compensation expense	13,525	8,419
Change in fair value of contingent consideration	—	2,562
Adjusted EBITDA (Non-GAAP)	$ (15,105)	$ (11,384)

1. Beginning in the fourth quarter of 2022, we began excluding interest income from the calculation of Adjusted EBITDA. The prior-year period presented herein has been recast to conform to the current period presentation.

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Appendix

Leadership Team Overview

MANAGEMENT TEAM

Derek Maetzold
Founder, Director, President and CEO

Frank Stokes
Chief Financial Officer

Toby Juvenal
Chief Commercial Officer

Kristen Oelschlager, RN, CHC
Chief Operating Officer

Robert Cook, PhD
Senior Vice President, Research & Development

Matthew Goldberg, MD
Medical Director

Alice Izzo
Senior Vice President, Marketing

BOARD OF DIRECTORS

- Dan Bradbury
- Derek Maetzold
- Mara Aspinall
- Brad Cole
- Tiffany Olson
- Miles D. Harrison
- Kimberlee Caple
- Ellen Goldberg