

› Empowering people, informing care decisions



November 2024

C/STLE
BIOSCIENCES

Disclaimers

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 positioning for continued growth and value creation; our estimated U.S. total addressable market for our commercially available tests; our ongoing studies generating data and their impact on driving adoption of our tests; study observations and interpretations of study data, including conclusions about the benefits and impact of our tests on treatment decisions and patient outcomes; and our ability to be net operating cash flow positive by the end of 2025; our future approach to capital allocation; our expected launch of our pipeline expansion by the end of 2025; and the timing and achievement of program milestones. The words “anticipates,” “can,” “could,” “estimates,” “expects,” “may,” “potential,” “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; our assumptions or expectations regarding continued reimbursement for our DecisionDx-SCC test at the current rate and reimbursement for our other products and subsequent coverage decisions, our estimated total addressable markets for our products and product candidates and the related expenses, capital requirements and potential needs for additional financing, the anticipated cost, timing and success of our product candidates, and our plans to research, develop and commercialize new tests and our ability to successfully integrate new businesses, assets, products or technologies acquired through acquisitions, the effects of macroeconomic events and conditions, including inflation and monetary supply shifts, labor shortages, liquidity concerns at, and failures of, banks and other financial institutions or other disruptions in the banking system or financing markets and recession risks, supply chain disruptions, outbreaks of contagious diseases and geopolitical events (such as the ongoing Israel-Hamas War and Ukraine-Russia conflict), among others, 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 anticipated 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, 2023, in our Quarterly Report on Form 10-Q for the period ended September 30, 2024, each filed or to be filed with the SEC, 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.

Disclaimers

Financial Information; Non-GAAP Financial Measures

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 GAAP net revenues to exclude net positive and/or net negative revenue adjustments recorded in the current period associated with changes in estimated 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 income (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. 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.

These non-GAAP financial measures are not meant to be considered in isolation or used as substitutes for net revenues, gross margin, or net income (loss) reported in accordance with GAAP; should be considered in conjunction with our financial information presented in accordance with GAAP; have no standardized meaning prescribed by GAAP; are unaudited; and are not prepared under any comprehensive set of accounting rules or principles. In addition, from time to time in the future, there may be other items that we may exclude for purposes of these non-GAAP financial measures, and we may in the future cease to exclude items that we have historically excluded for purposes of these non-GAAP financial measures. Likewise, we may determine to modify the nature of adjustments to arrive at these non-GAAP financial measures. Because of the non-standardized definitions of non-GAAP financial measures, the non-GAAP financial measure as used by us in this press release and the accompanying reconciliation tables have limits in their usefulness to investors and may be calculated differently from, and therefore may not be directly comparable to, similarly titled measures used by other companies. Accordingly, investors should not place undue reliance on non-GAAP financial measures. Reconciliations of these non-GAAP financial measures to the most directly comparable GAAP financial measures are presented in the tables at the end of this presentation.

Industry and Market Data

This presentation includes certain information and statistics obtained from third-party sources. The Company has not independently verified the accuracy or completeness of any such third-party information.

Registered Trademarks

DecisionDx-Melanoma, DecisionDx-CMSeq, i31-SLNB, i31-ROR, DecisionDx-SCC, MyPath Melanoma, DiffDx-Melanoma, TissueCypher, IDgenetix, DecisionDx-UM, DecisionDx-PRAME and DecisionDx-UMSeq are trademarks of Castle Biosciences, Inc.

OUR MISSION

Improving health
through **innovative tests**
that guide patient care

OUR VISION

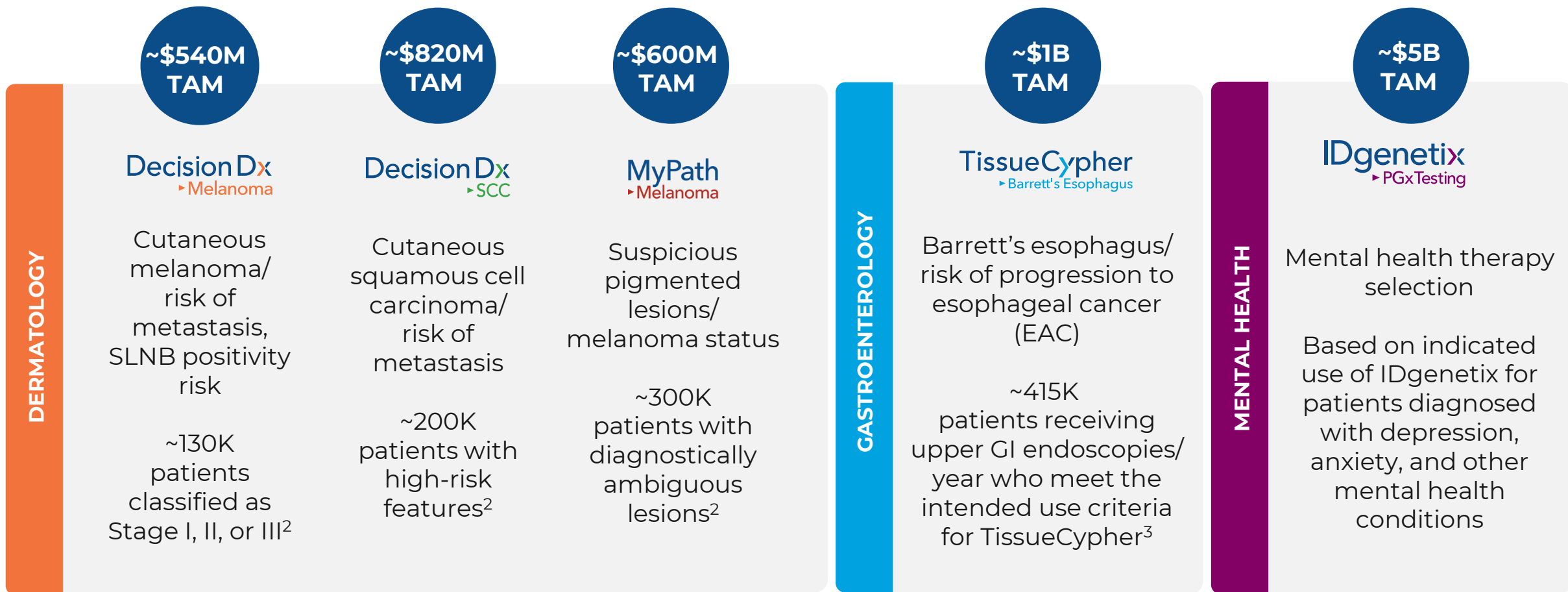
Transforming disease
management by keeping
people first: patients, clinicians,
employees, and investors



Proven strategy designed to drive value creation for our stakeholders

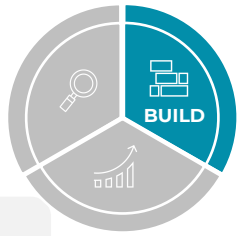


Estimated ~\$8B U.S. total addressable market¹ for commercially available tests



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).

Building evidence showing the value of our tests



DecisionDx ▶ Melanoma

Studies¹ show clinical use of our test is associated with improved melanoma specific outcomes, which means the test guides appropriate decisions and patients live longer. The test provides significantly better risk stratification than AJCC8 staging in patients with stage I cutaneous melanoma

DecisionDx ▶ SCC

Studies² demonstrating that our test can improve risk stratification when used in conjunction with staging, to help predict responsiveness to adjuvant radiation therapy (ART) and when used in conjunction with clinicopathologic factors in considering use of ART, can potentially lead to net annual Medicare healthcare savings of up to approximately \$972 million

TissueCypher ▶ Barrett's Esophagus

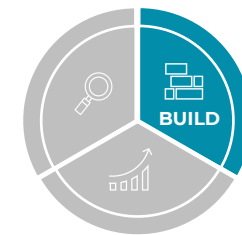
Ablation has been shown to stop progression to EAC but use is generally limited to clinicopathologically identified higher-risk patients.³ New pooled analysis⁴ and SRMA studies⁵ show that our test is a stronger identifier of higher risk disease compared to all clinicopathologic factors

IDgenetix ▶ PGx Testing

Randomized controlled study shows integrating drug-gene, drug-drug and lifestyle factors provides 75%⁶ more guided information compared to traditional drug-gene interactions alone

1. Podlipnik S, Martin BJ, Morgan-Linnell SK et al., Dhillon et al. *Archives of Derm Research* 2023 and Bailey et al. *JCO PO*, 2023; 2. Arron et al., Wysong A, Newman JG, Covington KR, et al., Gopal R, Marquardt M, Singh G, et al., Somani SK, Ibrahim SF, Tassavor M, et al., and Newman et al. *Head & Neck* 2021; Ruiz et al. *JAAD* 2022; Moody et al. accepted and Castle Biosciences data on file; 3. Cotton CC, et al. *Gastroenterology*. 2017; 4. Davison et al. *Clin Transl Gastroenterol* 2023; 5. Castle Biosciences data on file (Systematic Review and Meta-Analysis of TissueCypher's predictive performance in five completed clinical validation studies); 6. Cao et al., Psych Congress Annual Meeting 2023
EAC=esophageal adenocarcinoma

DecisionDx-Melanoma provides precise, personalized risk prediction for two critical clinical questions



Clinical use of DecisionDx-Melanoma is associated with improved patient survival



Individual risk of SLNB positivity

Individual risk of recurrence

3I-GEP
Class Score

i3I-SLNB

Ulceration
Breslow thickness
Age
Mitotic rate

i3I-ROR

Ulceration
Age
Breslow thickness
Mitotic rate
SLN status
Tumor location

Collaborative study with the National Cancer Institute's SEER Program Registries is the largest real-world study of GEP testing in melanoma (n=4,687):

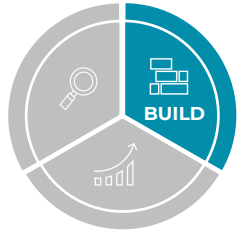
- SEER cohort of **unselected, prospectively** tested patients shows improved survival for patients tested with DecisionDx-Melanoma compared to untested patients with **29% lower 3-year melanoma-specific and 17% lower 3-year overall mortality**, and
- DecisionDx-Melanoma provided **significant, independent risk stratification** of patients with cutaneous melanoma

SLN- patients with a high-risk DecisionDx-Melanoma result had routine imaging surveillance added to their treatment plan. These patients:

- Had their recurrence detected **~10 months earlier**, with **62% lower tumor burden**
- Were more likely to **start immunotherapy** when offered (76.3% vs 67.9%)
- Saw **improved overall survival** outcomes at 45 months (86.8% vs 75%)

“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.”

DecisionDx-Melanoma significantly improves risk stratification in stage I melanoma compared to AJCC staging



DecisionDx-Melanoma compared to American Joint Committee on Cancer Staging Manual 8th Edition (AJCC8) staging for stage I cutaneous melanoma (CM) patients (n=6,883) in 2 cohorts analyzed recurrence-free survival and melanoma-specific survival. Study results demonstrated:

- DecisionDx-Melanoma **significantly improved patient risk stratification**, independent of AJCC8 staging in patients
- DecisionDx-Melanoma **provided greater separation** between high-risk (Class 2B) and low risk (Class 1A) groups than seen between AJCC8 stage IA and IB

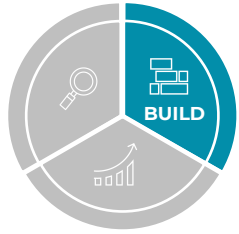
COHORT 1 – Combined

Combined cohort of stage I CM patients enrolled in previous retrospective and prospective studies from multiple centers (n=1,261)

COHORT 2 – NCI-SEER

Large, unselected real-world cohort of stage I CM patients from the SEER registry (n=5,651)

Evidence from prospective studies supporting DecisionDx-Melanoma demonstrates:



1

Physicians are using DecisionDx-Melanoma to inform clinical decisions about sentinel lymph node biopsy (SLNB) and **performing fewer SLNBs**

2

DecisionDx-Melanoma low-risk test results are **associated with very low SLNB positive outcomes**

3

DecisionDx-Melanoma low-risk, Class 1A patients who **forego an SLNB have high recurrence-free survival**

Advancing penetration of our tests with clinicians and payers



Expert Consensus & Guidelines¹

- DecisionDx-Melanoma: 2023 National Society for Cutaneous Medicine recommends use of GEP testing (DecisionDx-Melanoma) in the clinical assessment and management of CM
- DecisionDx-SCC: 2023 Expert consensus panel report recommends considering the test for SCC cases with at least one high-risk feature to maximize prognostic accuracy and utility
- TissueCypher: 2024 AGA Clinical Practice Guideline acknowledges that individuals who may be at increased risk of progression to esophageal cancer might be identified using tissue-based biomarkers, particularly TissueCypher

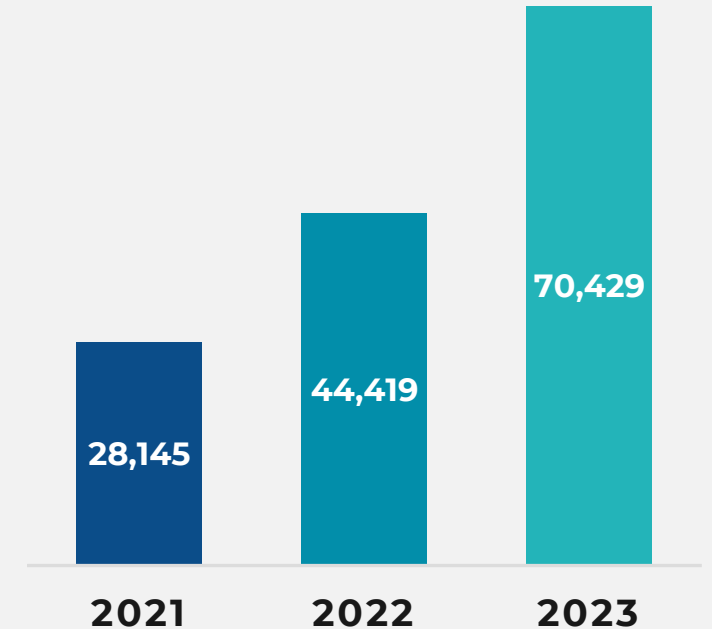
Reimbursement Strategy

- Increased total number of ADLTs to 5 by obtaining approval from CMS for DecisionDx-SCC
- Increased the CLFS payment rate for 2024 on 4 of our tests through the CLFS and PAMA rate-setting process, while maintaining value-based rates for our remaining tests
- Secured positive medical policies across all four therapeutic areas in 2024 (i.e., dermatology, gastroenterology, mental health and UM)

Castle Commercial Playbook

- Optimizing commercial team
- Continuing provider education
- Evolving our white glove go-to-market strategy
- Comprehensive digital strategy
- Robust patient advocacy strategy across all therapeutic areas

Total Test Report Volume



> Financials



Well positioned for continued value creation



Drive robust test volume growth



Maintain strong Adjusted Gross Margin



Goal to achieve operating cash flow positivity by the end of 2025



Maintain strong balance sheet

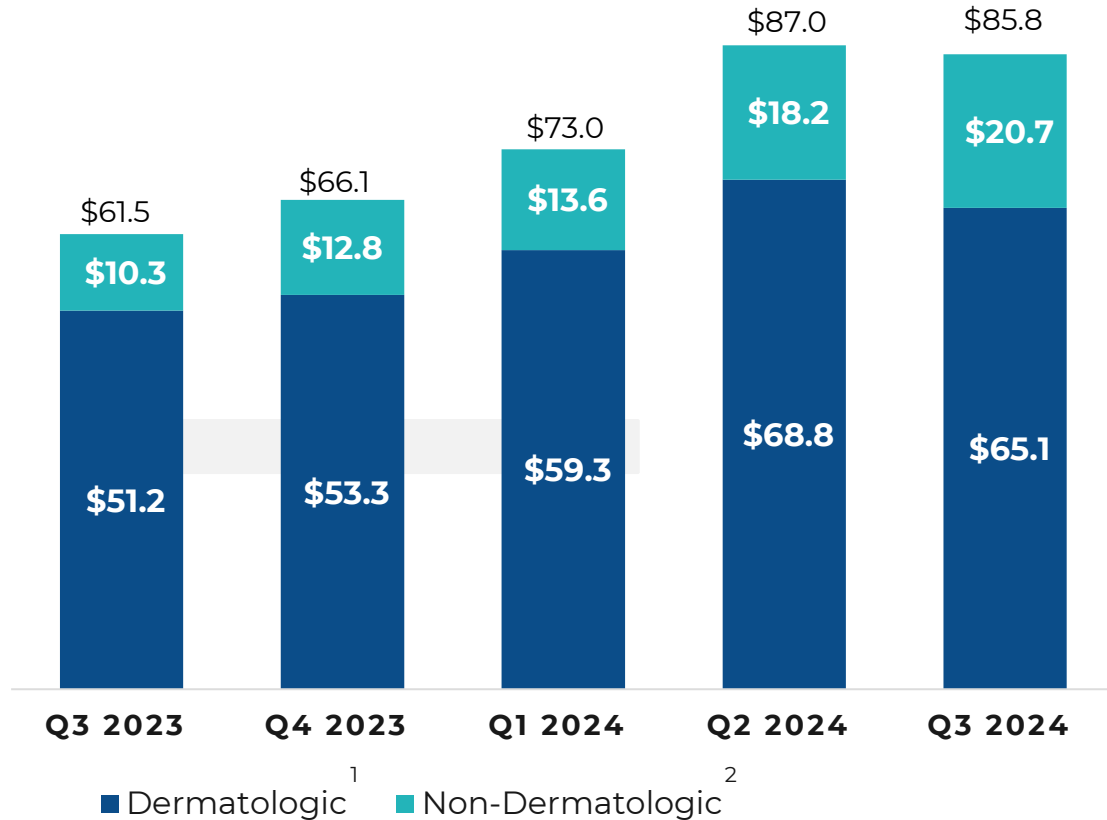


Follow disciplined capital allocation

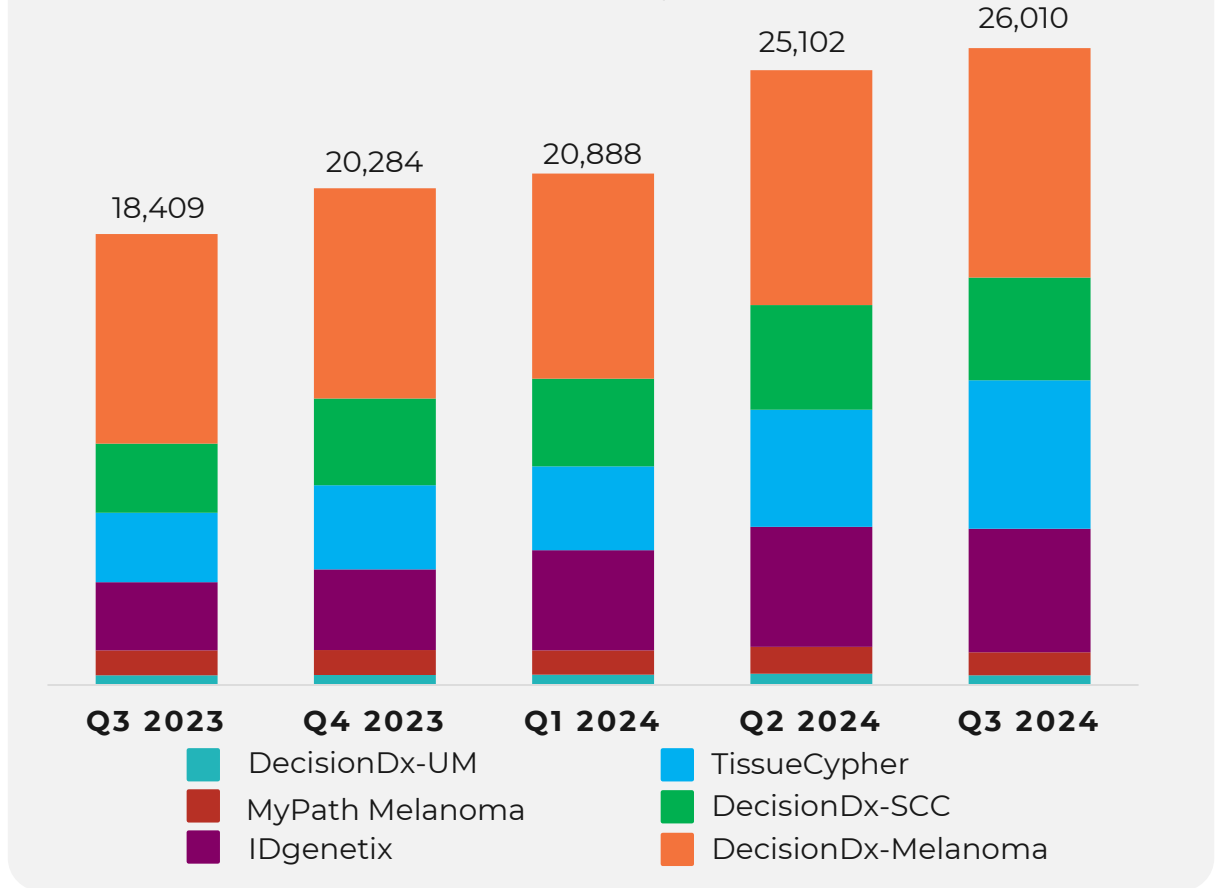


Drive robust test report volume and revenue growth

NET REVENUE BY QUARTER (\$M)



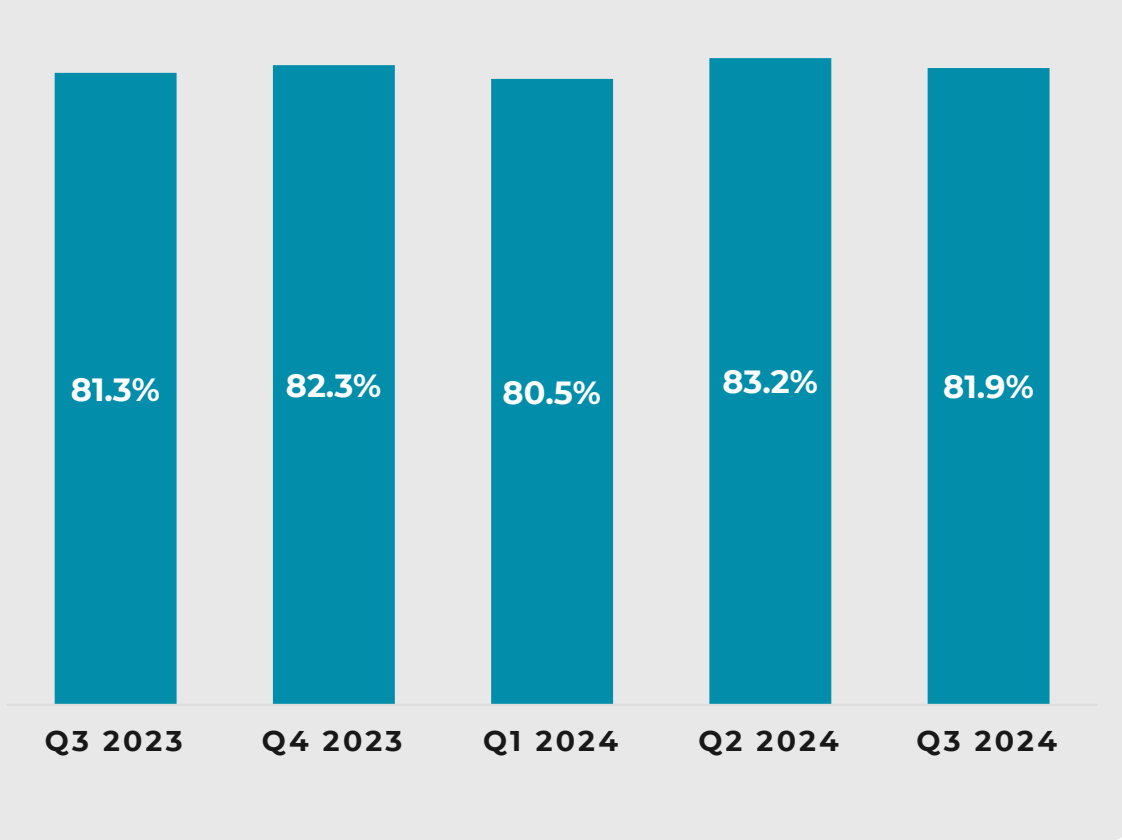
TOTAL TEST VOLUME BY QUARTER



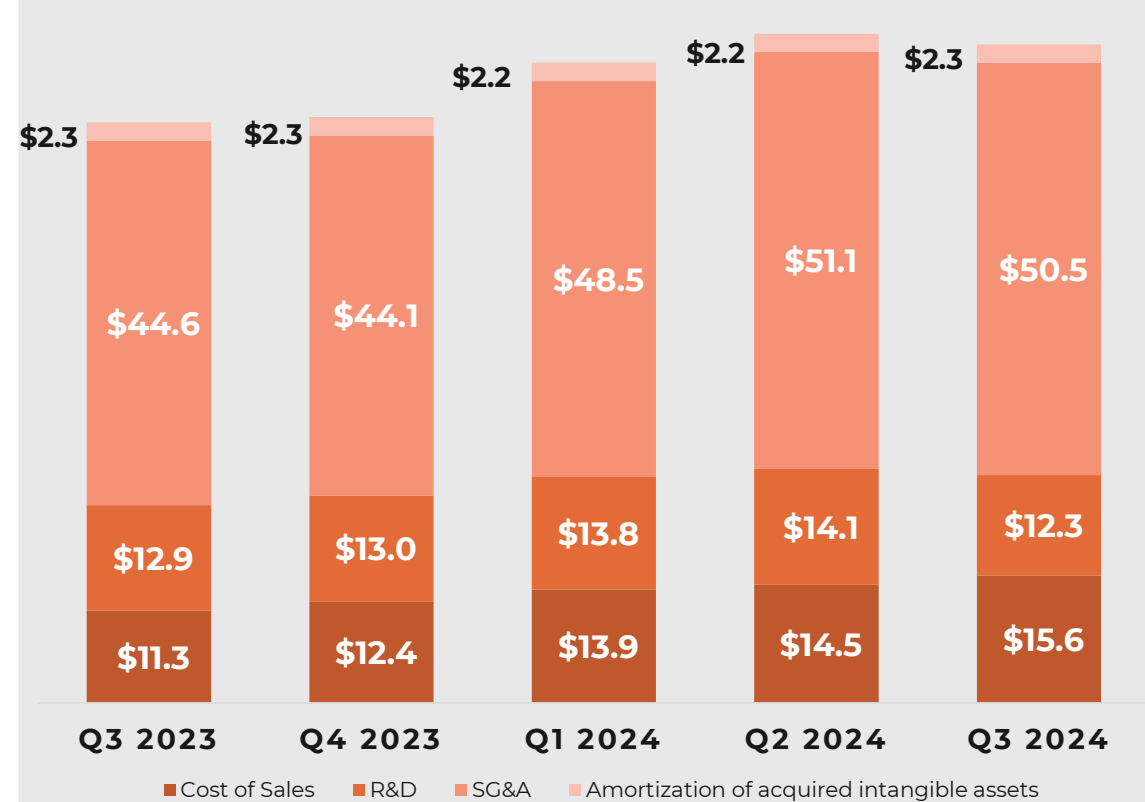


Maintain strong Adjusted Gross Margin

ADJUSTED GROSS MARGIN BY QUARTER^{1,2}



OPERATING EXPENSES BY QUARTER (\$M)³

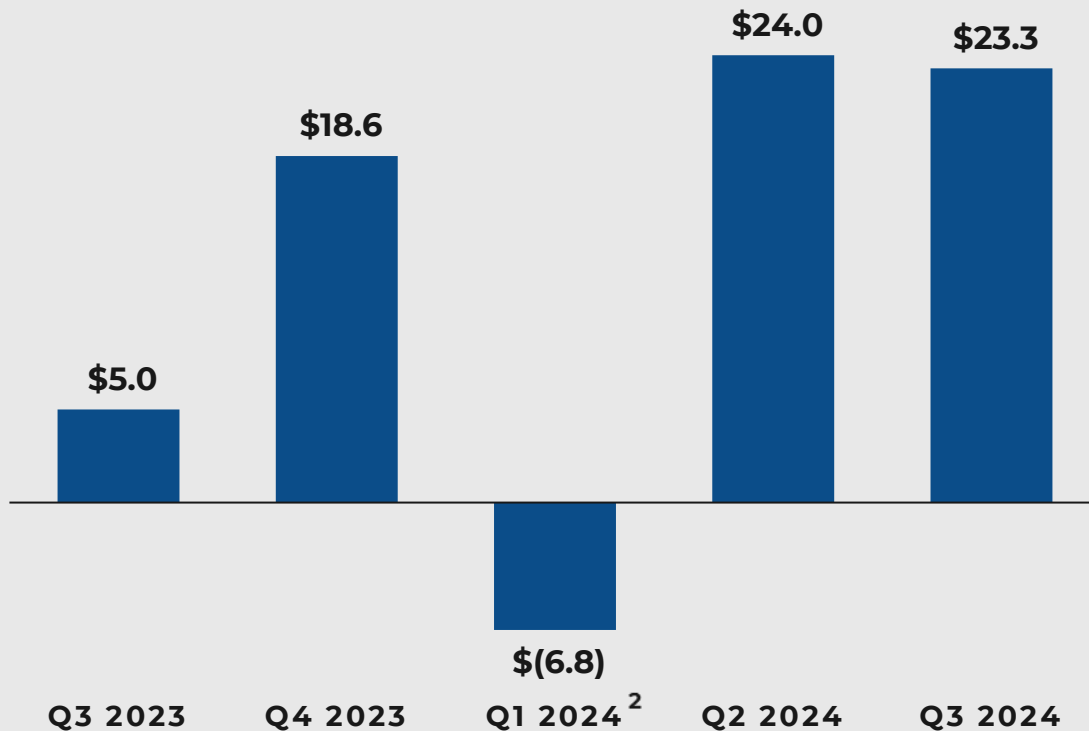




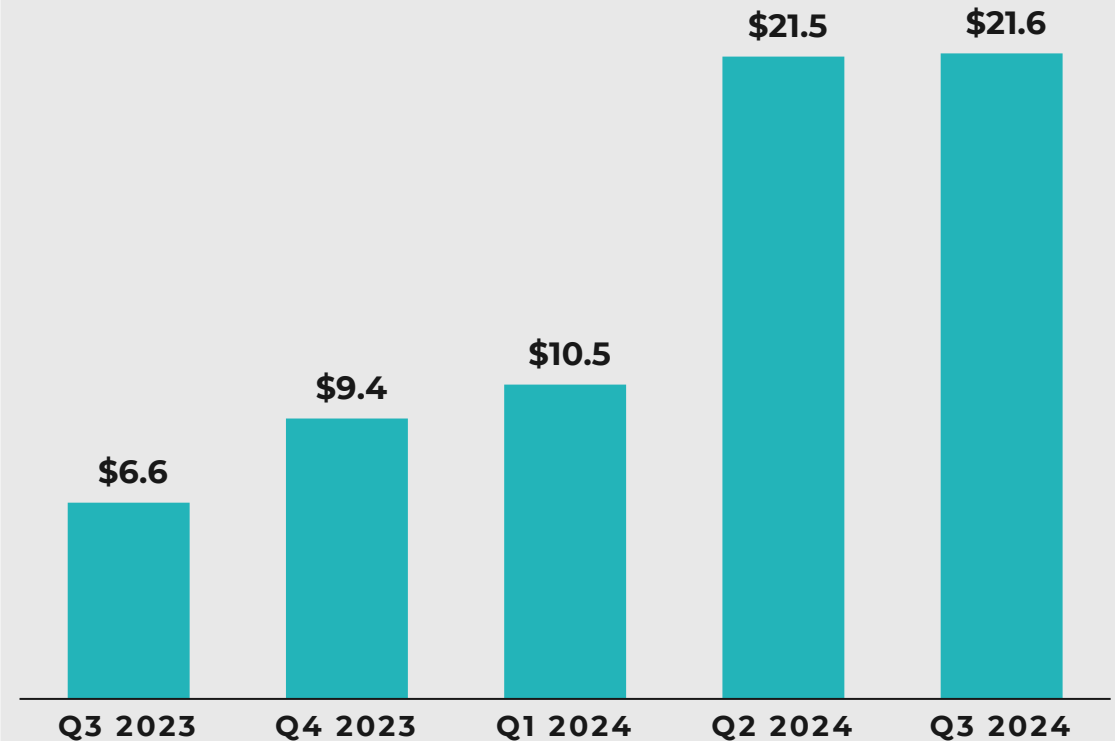
Improving operating cash flow and Adjusted EBITDA

Cash position of ~\$280M¹ supports growth initiatives

OPERATING CASH FLOW BY QUARTER (\$M)



ADJUSTED EBITDA BY QUARTER (\$M)^{3,4}



1. As of September 30, 2024; includes Cash, Cash Equivalents & Marketable Investment Securities
2. Net cash used in operating activities in Q1 2024 includes payout of annual bonuses as well as certain healthcare benefit contributions
3. Adjusted EBITDA is a non-GAAP measure. See non-GAAP reconciliations at the end of this presentation for a reconciliation of Adjusted EBITDA to its most closely comparable GAAP measure
4. Adjusted EBITDA excludes from net income (loss), interest income, interest expense, income tax expense (benefit), depreciation and amortization expense, stock-based compensation expense and change in fair value of contingent consideration



A disciplined approach to capital allocation

Commercial optimization

Focused R&D efforts to build evidentiary support and develop tests

As a lesser priority, strategic opportunities, including within our current therapeutic areas

> Appendix

DecisionDx-Melanoma

Provides comprehensive, personalized, genomic tumor information to guide management for patients with cutaneous melanoma

Clinical Validity, Utility and Demonstrated Patient Outcomes

Demonstrated clinical validity, utility and impact, backed by 50 peer-reviewed publications (as of February 2024), including two publications (Bailey et al. 2023 and Dhillon et al. 2023) demonstrating an association with testing and improved patient outcomes

SLNB Guidance and Patient Outcomes^{4,5}

DecisionDx-Melanoma successfully identified patients with T1 tumors with a low risk of SLN positivity who can safely forego SLNB while maintaining high survival rates in a prospective multicenter study and can reduce SLNB-associated complications and healthcare costs.

1. Data as of June 30, 2024, from third-party data and management estimates; 2. Dillon et al. 2022
3. Data as of September 30, 2024; 4. Marks, The i31-GEP identifies patients with T1 cutaneous melanoma who can safely avoid sentinel lymph node biopsy: Results from a prospective, multicenter study. Video abstract presented at: 2024 American Society for Dermatologic Surgery (ASDS) Annual Meeting; 5. Guenther JM, et al. Patients who forego sentinel lymph node biopsy after 31-GEP testing are not harmed: A prospective, multicenter analysis. Poster presented at: 20th European Association of Dermato-Oncology (EADO) Congress
SLN(B)=sentinel lymph node (biopsy)



~30%

market penetration¹

50%

Demonstrated change in management for 1 of 2 patients tested²

~183,000

patients with a clinical DecisionDx-Melanoma order from ~14,550 clinicians³

DecisionDx-SCC

Identifies the risk of metastasis in patients with squamous cell carcinoma (SCC) and one or more risk factors

Clinical Validity and Utility

Demonstrated validity, utility and impact, backed by 22 peer-reviewed publications, including data showing that DecisionDx-SCC can significantly impact patient management plans in a risk-appropriate manner within established guidelines

Real-World Use Framework

Study in *Clinical, Cosmetic and Investigational Dermatology* highlights a clinician-derived, real-world algorithm that provides a framework to incorporate DecisionDx-SCC test results into clinical practice within NCCN guidelines recommendations



~200,000

patients diagnosed annually with SCC and classified as high risk in the U.S.

~75%

of clinicians ordering DecisionDx-SCC also ordered DecisionDx-Melanoma²

Up to ~\$972M

net annual Medicare savings that could be realized by using DecisionDx-SCC to guide adjuvant radiation therapy decisions¹

MyPath Melanoma

Aids in the diagnosis and management for patients with ambiguous melanocytic lesions

Clinical Validity and Utility

Demonstrated validity, utility and impact, backed by 17 peer-reviewed publications demonstrating the performance and utility of the test in providing objective information to aid in diagnosis in ambiguous melanocytic lesions

Guideline Support

- National Comprehensive Cancer Network guidelines for cutaneous melanoma in the principles for molecular testing
- American Society of Dermatopathology in the Appropriate Use Criteria for ancillary diagnostic testing
- American Academy of Dermatology guidelines of care for the management of primary cutaneous melanoma

~300,000

patients each year present with a diagnostically ambiguous lesion

>45,000

lesions tested clinically¹

17

peer-reviewed publications

TissueCypher

A leading risk-stratification test designed to predict risk of progression to esophageal cancer in patients with Barrett's esophagus

Clinical Validity and Utility

Demonstrated validity, utility and impact, backed by 14 peer-reviewed publications demonstrating the ability and performance of the test in risk-stratifying patients with Barrett's esophagus to guide risk-appropriate treatment decisions

Recognition from AGA

2024 Clinical Practice Guideline acknowledges that individuals who may be at increased risk of progression to esophageal cancer might be identified using tissue-based biomarkers, particularly TissueCypher

2022 Recognized in the Clinical Practice Update on New Technology and Innovation for Surveillance and Screening in Barrett's Esophagus as a tool that may be used by physicians to risk stratify non-dysplastic patients

~415,000

patients receiving upper GI endoscopies per year who meet intended use criteria for TissueCypher

1 in 40

patients progress to esophageal cancer within 5 years (among BE patients)¹

14

peer-reviewed publications

IDgenetix

Advanced pharmacogenomic (PGx) test designed to guide medication selection and management for patients with neuropsychiatric conditions, such as depression and anxiety

Advanced PGx

- Demonstrated clinical validity, utility and impact, backed by 19 peer-reviewed publications
- Eliminate trial and error prescribing
- Received 2024 MedTech Breakthrough Award for “Best Overall Mental Health Solution”

Easy to Use

- 10 mental health and pain conditions in one report
- Collection of DNA sample via simple cheek swab
- 3-5 days to receive test report on average
- Specialized sales and medical science liaison support



3 in 1 test

- drug-gene interactions
- drug-drug interactions
- lifestyle factors

2X

improved chance of medication response vs. control¹

>2.5X

improved chance of remission of depression symptoms vs. control¹

DecisionDx-UM

The standard of care for evaluating metastatic risk in uveal melanoma

Clinical Validity and Utility

Demonstrated validity, utility and impact, backed by 25+ peer-reviewed publications, which included more than 5,000 patients, representing the largest body of evidence for a molecular prognostic test in this field

Standard of Care

- Utilized in approximately 80% of newly diagnosed patients
- Favorable reimbursement profile – covered by Medicare and more than 100 private insurers
- Included in NCCN Guidelines and considered standard of care

~8 in 10

patients diagnosed with UM in the U.S. receive the test as part of their diagnostic workup

~2,000

patients diagnosed in the U.S. annually

25+ peer-reviewed publications

Inflammatory Skin Disease

Pipeline program to develop a genomic test aimed at guiding systemic therapy selection for patients with moderate-to-severe atopic dermatitis (AD), psoriasis (PSO) and related conditions

- Identified distinct gene expression profiles of response to both AD and PSO therapies, in addition to identifying distinct gene expression profiles for AD, PSO, and mycosis fungoides (MF) lesions
- Test results could empower clinicians to tailor therapy choices for patients by considering their molecular profiles, potentially sparing patients from undergoing numerous ineffective and costly medication trials before discovering an effective treatment to manage their symptoms

Anticipated Program Milestones

- **Q423:** early discovery data presented
- **2H24:** development data expected
- **By end of 2025:** target launch

39

Active sites¹

>1,100

Patients enrolled^{1,2}

Reconciliation of Non-GAAP Financial Measures (Unaudited)

The tables below present the reconciliation of Adjusted Revenues and Adjusted Gross Margin, which are non-GAAP financial measures. See disclaimer slide for further information regarding the Company's use of non-GAAP financial measures.

(In thousands)	Three months ended				
	Sep. 30, 2024	Jun. 30, 2024	Mar. 31, 2024	Dec. 31, 2023	Sep. 30, 2023
Adjusted Revenues					
Net revenues (GAAP)	\$85,782	\$87,002	\$72,974	\$66,120	\$61,493
Revenue associated with test reports delivered in prior periods	552	(363)	(1,656)	4,086	(883)
Adjusted Revenues (Non-GAAP)	\$86,334	\$86,639	\$71,318	\$70,206	\$60,610
Adjusted Gross Margin					
Gross margin (GAAP) ¹	\$67,901	\$70,236	\$56,833	\$51,426	\$47,902
Amortization of acquired intangible assets	2,272	2,247	2,247	2,271	2,272
Revenue associated with test reports delivered in prior periods	552	(363)	(1,656)	4,086	(883)
Adjusted Gross Margin (Non-GAAP)	\$70,725	\$72,120	\$57,424	\$57,783	\$49,291
Gross margin percentage (GAAP) ²	79.2%	80.7%	77.9%	77.8%	77.9%
Adjusted Gross Margin percentage (Non-GAAP)³	81.9%	83.2%	80.5%	82.3%	81.3%

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 EBITDA, which is a non-GAAP financial measure. See disclaimer slide for further information regarding the Company's use of non-GAAP financial measures.

<i>(In thousands)</i>	Three months ended				
	Sep. 30, 2024	Jun. 30, 2024	Mar. 31, 2024	Dec. 31, 2023	Sep. 30, 2023
Adjusted EBITDA					
Net income (loss)	\$2,269	\$8,920	\$(2,534)	\$(2,580)	\$(6,905)
Interest income	(3,404)	(3,144)	(2,996)	(3,119)	(2,769)
Interest expense	201	270	14	2	2
Income tax expense (benefit)	6,013	(1,034)	45	39	32
Depreciation and amortization expense	3,541	3,348	3,340	3,224	3,174
Stock-based compensation expense	13,027	13,179	12,675	11,802	13,043
Adjusted EBITDA (Non-GAAP)	\$21,647	\$21,539	\$10,544	\$9,368	\$6,577

➤ Thank You

