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Investor Day

September 20, 2022

Patient Testimonial

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: 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, including our revenue outlook for the 2022 fiscal year; our expectations regarding timelines and milestones for our dermatologic, gastrointestinal and mental health franchises, including timeframes for expected material revenue contributions; the potential of systemic therapy guidance tools to streamline therapeutic interventions for patients and avoid ineffective, expensive medication courses, and achieve faster responses times, healthcare savings and improved patient outcomes and quality of life; our expectation that the future of mental health treatment will include PGx as a fundamental part of everyday, best practice medical care; our three-year projections for revenue, adjusted gross margin, other operating expenses and net operating cash flow; our expectation that each of our tests will reach at least 50%-60% penetration at maturity; our expectation that we will achieve net operating cash flow positivity by 2025, including our common-size P&L model at maturity; our expectations that our growing revenue base will enable us to continue and build on our strong gross margin performance, and that our focused growth investments will contribute to long-term profitability; our milestone expectations regarding the Palmetto/MolDx draft LCD, finalization of a Palmetto/Meridian LCD for DiffDx-Melanoma by the end of Q2 2023, publication of a collaborative NCI study showing higher melanoma specific survival for patients tested with DecisionDx-Melanoma by late 2022 or early 2023, new GI and MyPath/DiffDx commercial team expansion increasing productivity in late Q1/early Q2, rationalization of our San Diego lab by the end of 2022 and credentialing for IDgenetix United Healthcare coverage completed by late 2022 or 2023; components and drivers of our near- to mid-term growth and mid- to long-term growth; the impact, accuracy and effectiveness of our commercial and pipeline tests on physicians, patients and their treatment plans, and their individual or collective impact on our prospects and plans, including any objectives of management related thereto; the ability of our tests to provide valuable, clinically actionable information to clinicians and patients, improve health and guide patient care; expected expansion of outside sales territories; our progress roadmaps for our tests; expected launch dates for tests in our pipeline expansion and estimates regarding their total addressable markets or future success; expectations regarding LCD effective timeframes and reimbursement capabilities; increases in headcount in furtherance of our pipeline tests, clinical research and development and other expected drivers of growth, as well as efficiencies and synergies from capital expenditures related to expansion of lab facilities contributing to our growth; our ability to develop clinical evidence and publish peer-reviewed reports and studies that increase adoption among providers and commercial payors; estimated healthcare cost savings provided by our tests; the ability of our risk stratification tests to classify risk of metastasis in ways that better support risk-appropriate treatment than reliance on traditional clinicopathologic risk factors alone; program milestones for our pipeline test designed to predict systemic therapy response and the potential of systemic therapy guidance tools to streamline therapeutic interventions for patients and avoid ineffective, expensive medication courses; integration timelines, growth expectations and strategic opportunities for our TissueCypher test and GI franchise, and our IDgenetix test and our mental health franchise; and our ability to integrate our recent acquisitions into our existing business and the ability of such acquisitions to complement our existing business. The words "anticipates," "believes," "can," "estimates," "expects," "may," "plans," "potential," "will" 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 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 Quarterly Report on Form 10-Q for the three months ended June 30, 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.

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Agenda

All times Eastern

4:00-4:05pm DecisionDx-Melanoma Patient Testimonial
4:05-4:10pm Frank Stokes, Chief Financial Officer
4:10-4:30pm Derek Maetzold, Founder, President & Chief Executive Officer
4:30-5:00pm Brent Moody, M.D., F.A.C.P., F.A.A.D., Skin Cancer Surgery Center, Nashville, TN
5:00-5:15pm Matthew Goldberg, M.D., F.A.A.D., Medical Director
5:15-5:30pm Craig Munroe, M.D., GI Medical Director
5:40-5:55pm Robert Cook, Ph.D., Senior Vice President, R&D
6:00-6:20pm Frank Stokes
6:20-6:30pm Derek Maetzold
6:30pm Q&A with Maetzold, Stokes, Goldberg & Munroe

Derek Maetzold
Founder, President & Chief Executive Officer

Brent Moody, M.D., F.A.C.P., F.A.A.D.
Skin Cancer Surgery Center, Nashville, TN

Frank Stokes
Chief Financial Officer

Matthew Goldberg, M.D., F.A.A.D.
Medical Director

Craig Munroe, M.D.
GI Medical Director

Robert Cook, Ph.D.
Senior Vice President, R&D

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Derek Maetzold

Mission

Improving health through innovative tests that guide patient care

Vision

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

Values

ExCIITE: Excitement, Collaboration, Integrity, Innovation, Trust and Excellence

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Castle Is Focused on Improving Health through Innovative Tests That Guide Patient Care

Dermatology

- DecisionDx-Melanoma
- DecisionDx-SCC
- MyPath | DiffDx-Melanoma

Uveal Melanoma

- DecisionDx-UM

Gastroenterology

- TissueCypher-Barrett's Esophagus

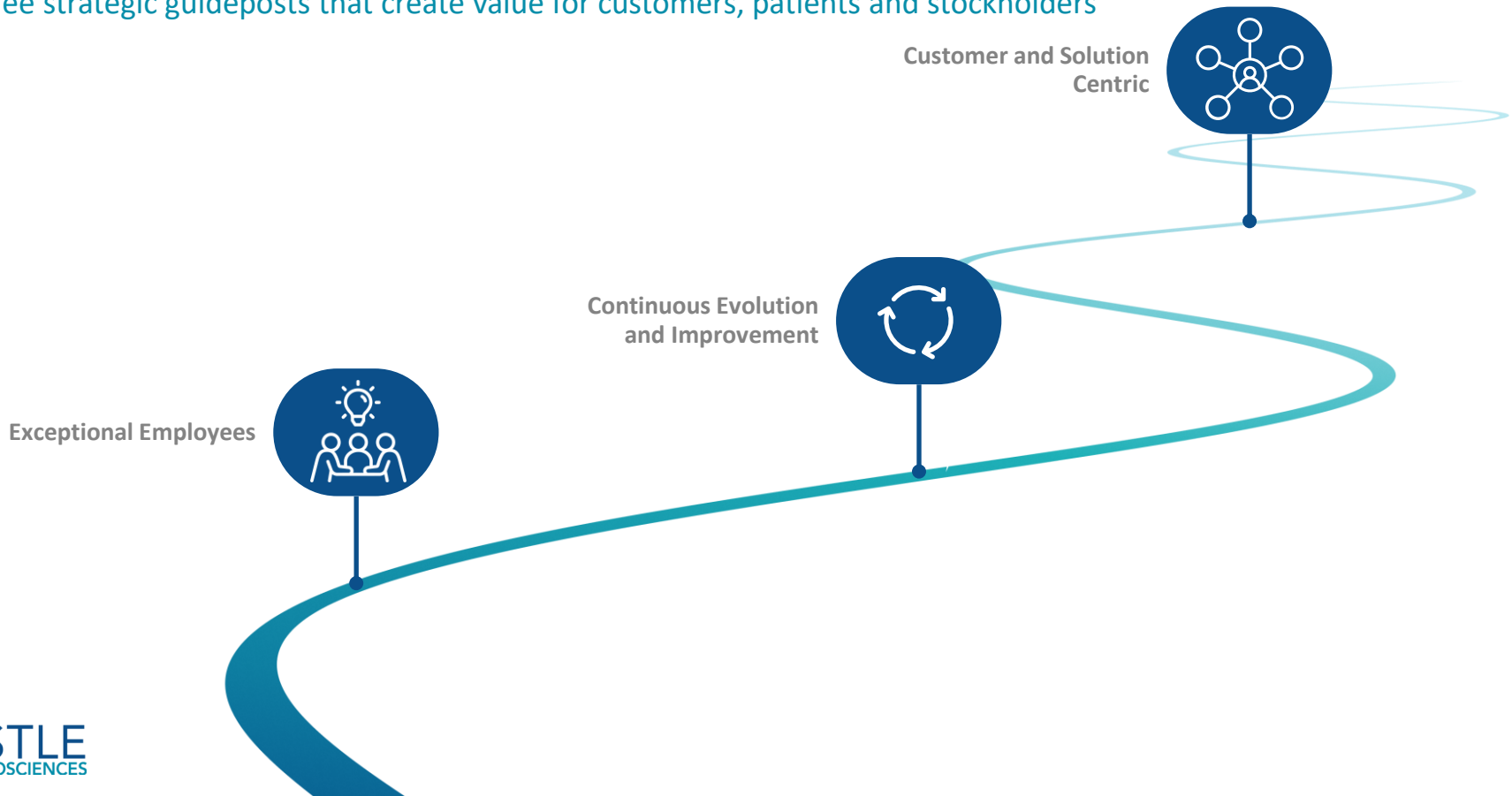
Mental Health

- IDgenetix

Portfolio of innovative tests designed to guide patient care

Castle Is Focused on Improving Health through Innovative Tests That Guide Patient Care

Three strategic guideposts that create value for customers, patients and stockholders



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Consistent Execution Furthers Our Leading Position in Dermatology and the Dx Space

Exceptional Employees

- Leadership development for all people leaders
- High retention
  - 2020: 94% retention rate; 4% regrettable turnover rate
  - 2021: 90% retention rate; 2% regrettable turnover
- Engagement scores from employee survey
  - 2021: 83% engagement score, compared to healthcare benchmark of 66%
  - 2022: 81% engagement score, compared to healthcare benchmark of 53%
- Defined career pathways

Continuous Evolution and Improvement

- Evolution of 31-GEP → i31-GEP
- Driving clinical value:
  - Robust, consistent performance data
  - Reproducible clinical impact data
  - Ultimately, improved outcomes (e.g., NCI/SEER collaboration)
- High impact, innovative, proprietary pipeline tests in development
- Harnessing communication flow (e.g., EHR integration and provider portal access)

Customer and Solution Centric

- More value for clinicians (multiple tests in a single call point)
- Acquired MyPath in May 2021 (combined with DiffDx workflow – actionable results more than 98% of the time[1])
- TissueCypher acquired in Dec. 2021; first-in-class test for Barrett's esophagus
- IDgenetix acquired in April 2022 – mental health PGx test with BOTH drug-drug and drug-gene interaction

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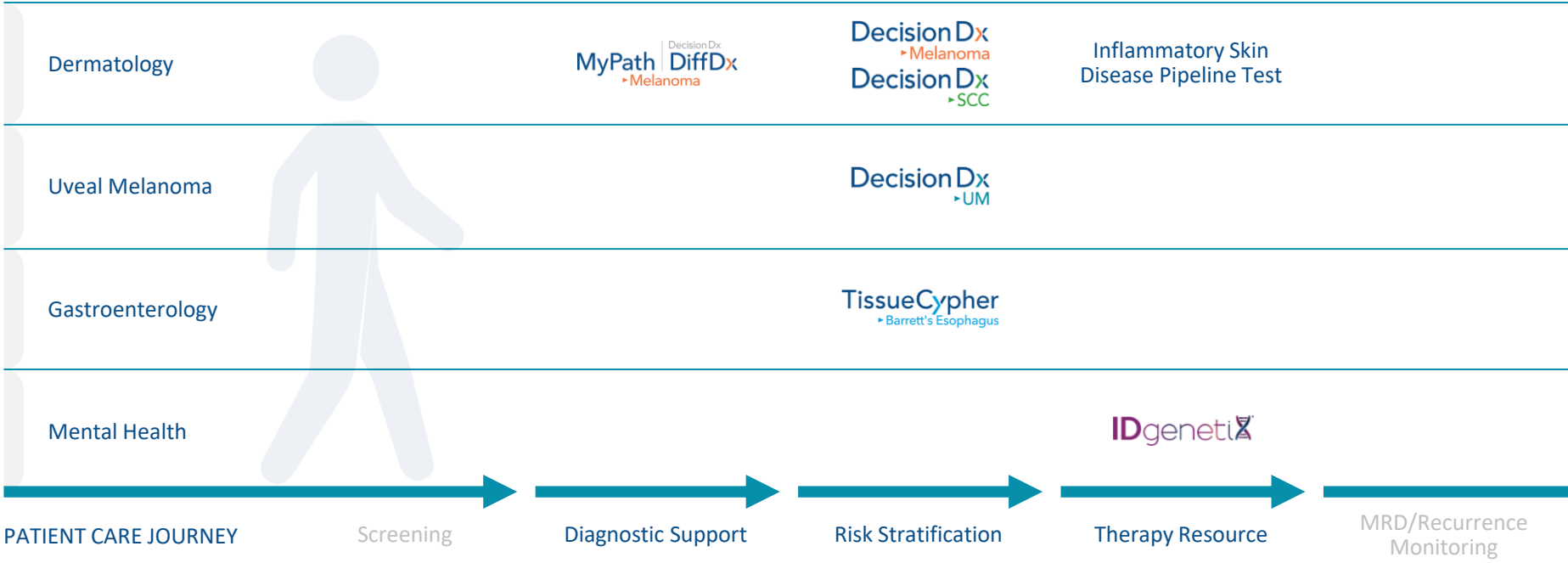
[1]Goldberg et al. *SKIN* 2021: s79

Answering Clinical Questions to Guide Care along the Patient Journey

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



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

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[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

Dermatology Playbook

2023 and Beyond

- Target Dermatologists, Surgeons, Dermatopathologists
- Evidentiary Development
- Commercial Team Expansion
- Differentiation and Innovation
- Guidelines and Reimbursement
- Digital Marketing

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GI Playbook

2023 and Beyond

- Commercial Team Expansion
- Drive Awareness Through Refined Messaging
- GI Outreach and Education
- Target Accounts Include Community Practice and Academic Medical Centers
- Digital Marketing

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Mental Health Playbook

2023 and Beyond

- Strengthen Leadership Team and Refresh Field Training
- Focus on Older Population Who Benefit Most from Unique Feature of Drug-Drug Interactions
- Expand Publications from Strong RCT Data to Continue Differentiation from Competitors
- Target Psychiatry Practices, Other High Prescribers of Mental Health Medications, Long-Term Care Facilities
- Digital Marketing

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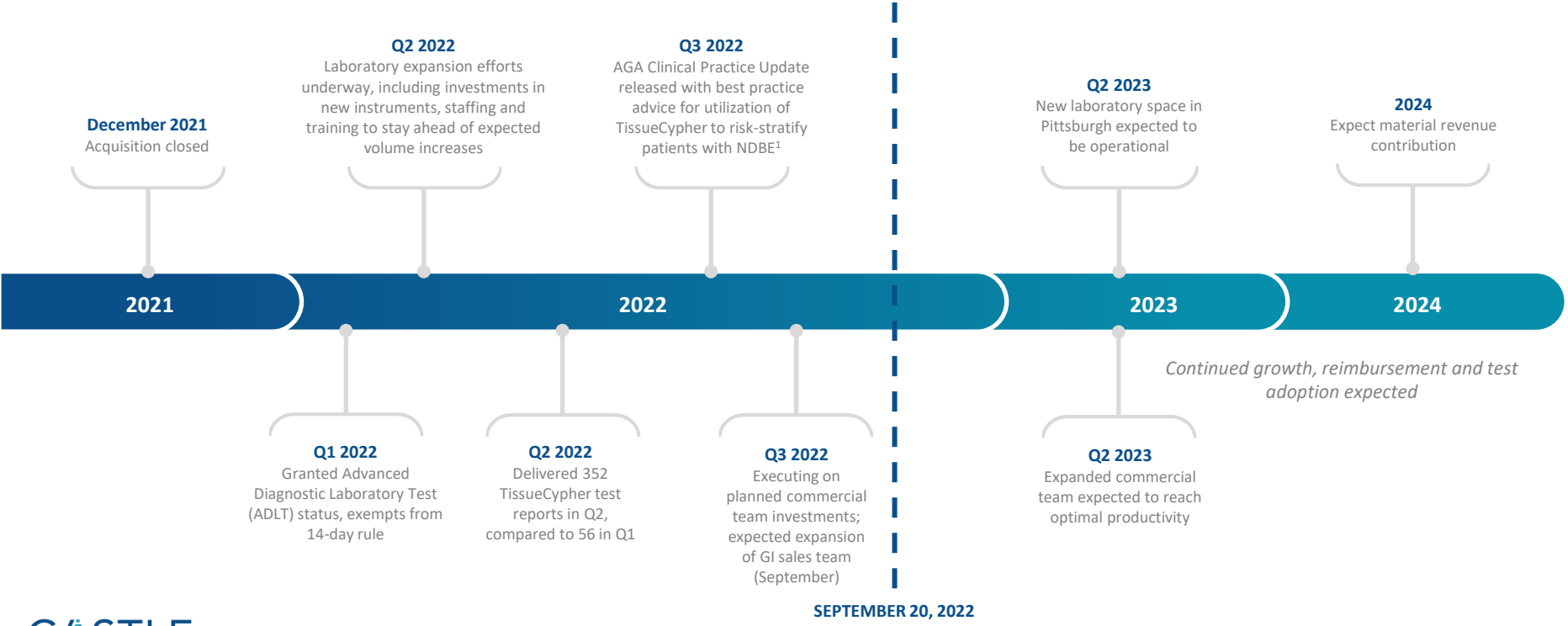
TissueCypher Acquisition Expected to Contribute Materially to Revenue in 2024 and Beyond

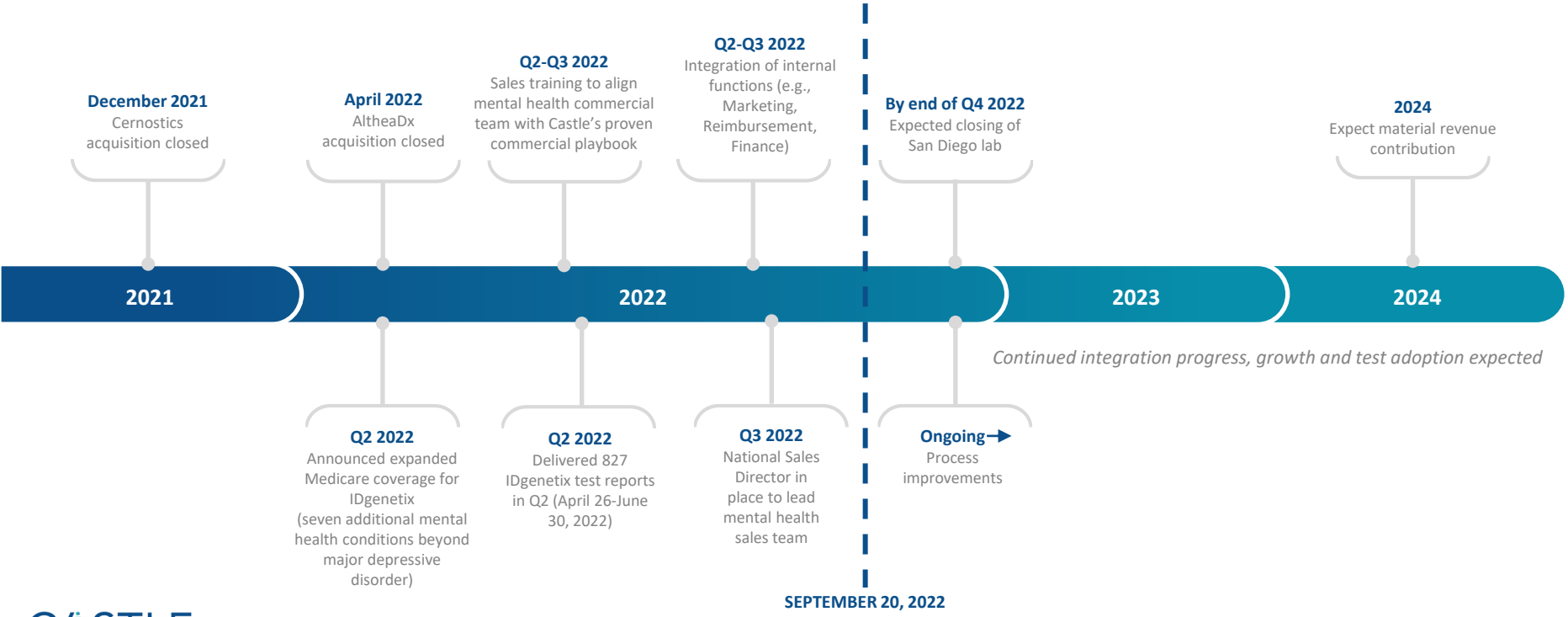
Significant milestones of integration plan achieved ahead of schedule



[1]NDBE=Non-dysplastic Barrett's esophagus

IDgenetix Acquisition Expected to Contribute Materially to Revenue in 2024 and Beyond

Integration plans on track with significant milestones already achieved



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Brent Moody, M.D., F.A.C.P., F.A.A.D.

Skin Cancer Surgery Center, Nashville, TN

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DecisionDx ▸Melanoma

About Melanoma

Skin cancer is the most common of all cancers

Basal Cell
8/10

Squamous Cell
2/10

Melanoma, Merkel cell carcinoma, Kaposi sarcoma, Cutaneous lymphoma
<1%

Melanoma ***accounts for less than 1% of skin cancers*** and is the ***second most frequent cause of skin cancer deaths***

Melanoma is the ***5th most commonly diagnosed cancer***

~7,500 melanoma deaths/year in the U.S.; ***five-year median survival is 93%***

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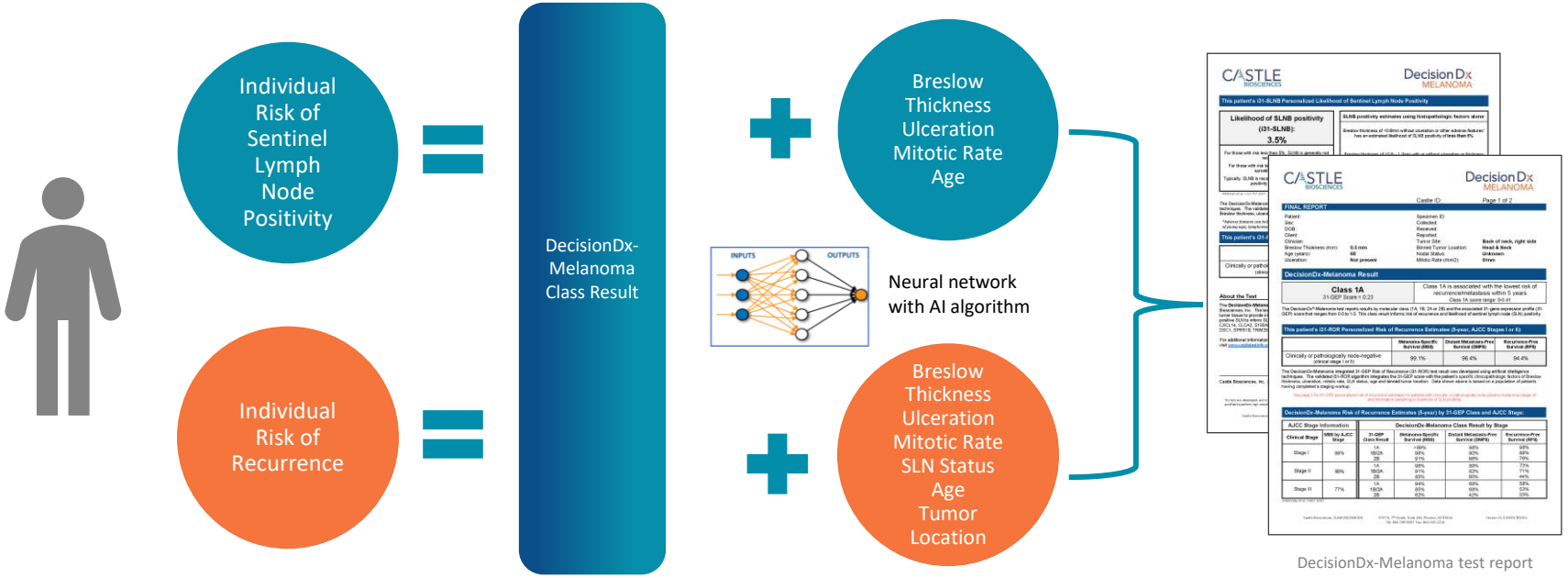
https://www.cancer.org/cancer/basal-and-squamous-cell-skin-cancer/about/what-is-basal-and-squamous-cell.html; www.cancer.net/cancer-types/skin-cancer-non-melanoma/introduction

DecisionDx-Melanoma Provides Answers for Two Critical Clinical Questions



DecisionDx-Melanoma test report

DecisionDx-Melanoma test results predict a patient's individual risk of recurrence and individual risk of sentinel lymph node positivity

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Whitman et al. *JCO PO* 2021; Jarell et al. *JAAD* 2022

Staging and Prognosis

Why?

We stage tumors in an effort to:

Predict biologic behavior (recurrence, metastasis, death)

Determine appropriate treatment and follow up

ALTER outcome by treating early to reduce likelihood of death

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Melanoma Staging Gaps

1. Too many deaths from the Stage I group
2. Stage IIB and IIC patients do worse than Stage IIIA patients

Can we do better? Time to update our thinking?

Rene Laenec
The first to distinguish melanoma as a separate disease

William Norris
The first to observe the heterogenic nature of some melanoma tumors

Robert Carswell
The term melanoma was introduced

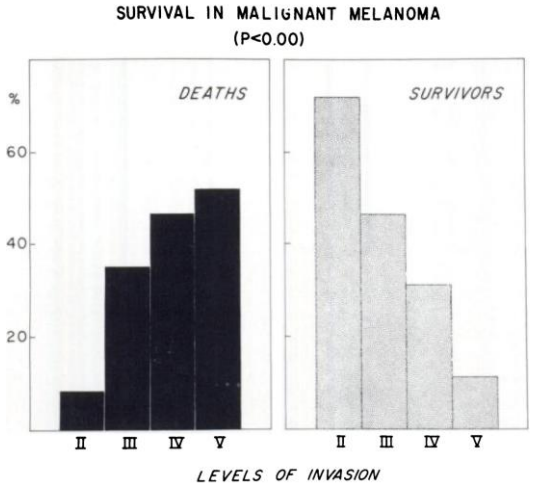
Samuel Cooper
Formally acknowledged that advanced melanoma was untreatable and that "the only chance for benefit depends on early removal of the disease"

Herbert Snow
Expressed the benefits of removing the tumor and surrounding glands as a method of prophylaxis in the treatment of melanoma

Staging and Prognosis – Past

Dr. Wallace Clark (1924-1997) USA

"Clark's Level" 1969: Used in older versions of AJCC staging



[CANCER RESEARCH 29, 705–726, March 1969]

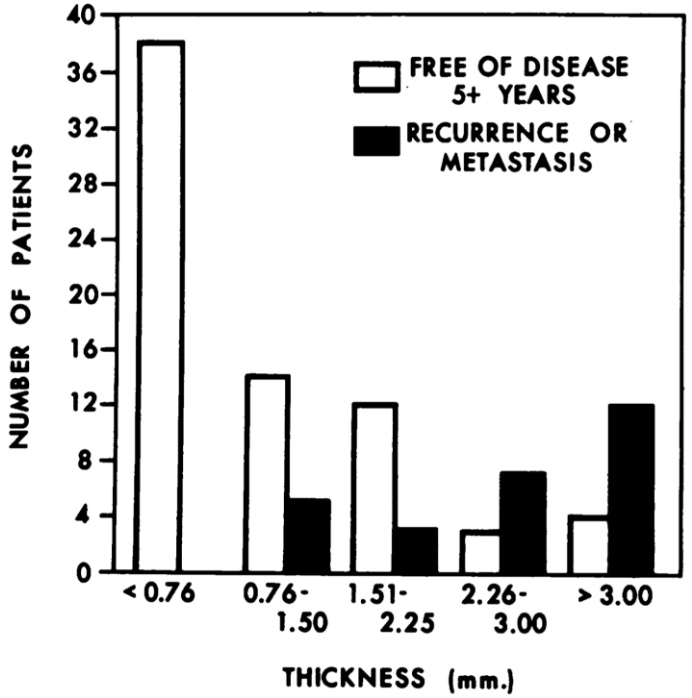
The Histogenesis and Biologic Behavior of Primary Human Malignant Melanomas of the Skin[1]

Wallace H. Clark, Jr.,[2] **Lynn From, Evelina A. Bernardino, and Martin C. Mihm**

Departments of Pathology and Dermatology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114

"It has been quite difficult to explain this apparent striking discrepancy in survival rates of malignant melanoma"

Can We Do Better? Dr. Breslow Thought So 1970…



Thickness, Cross-Sectional Areas and Depth of Invasion in the Prognosis of Cutaneous Melanoma

ALEXANDER BRESLOW,* M.D.

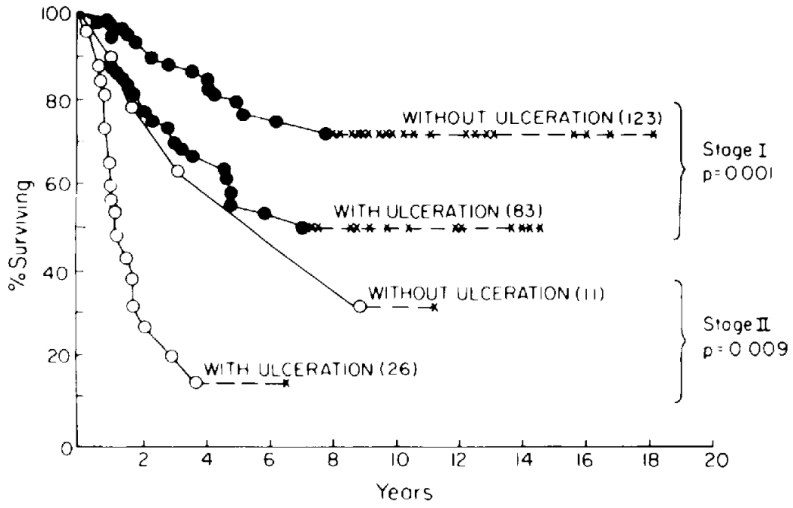
From The George Washington University School of Medicine, Washington, D. C.

"Cutaneous melanoma is a most unpredictable lesion"

Staging and Prognosis – Past

Dr. Charles Balch (MD Anderson)

Ulceration 1980



The Prognostic Significance of Ulceration of Cutaneous Melanoma

CHARLES M. BALCH, MD, FACS,* JAMES A. WILKERSON, MD, TARIQ M. MURAD, MD, PHD, SENG-JAW SOONG, PHD, ANNA LEE INGALLS, RN, AND WILLIAM A. MADDOX, MD, FACS

Cancer 45:3012–3017, 1980.

Staging and Prognosis – Present

AJCC 8:

- Breslow Thickness paper published in 1970 (meaningfully integrated into staging in 1983)
- Ulceration – 1980 described (added to staging in 2001)
- Lymph node status
- Distant metastasis

Factors used in prior staging systems: mitotic rate, level of invasion, site of visceral metastasis, lymph node minutia

Staging and Prognosis – Future

- Current melanoma staging relies upon factors that are 40 years old (ulceration) and 50 years old (Breslow thickness)
- These are **STILL CRITICALLY IMPORTANT**

Key Questions:

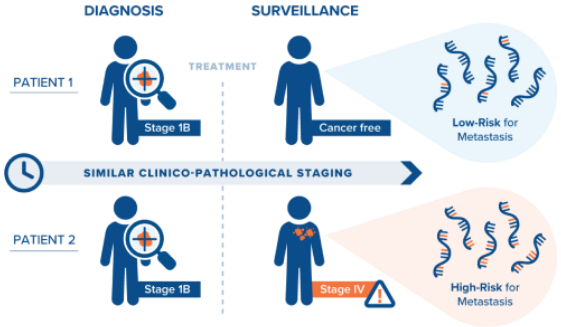
- What explains variation in outcome within a stage (intra-stage variability)?
- Why do some early-stage patients do poorly, and why do some late-stage patients seem to beat the odds?

Staging and Prognosis – Future

- Adding gene expression profiling (GEP) to traditional risk factors to better risk stratify patients, to better predict biologic behavior of the tumor
- In other cancer types, GEP is standard practice:
  - Uveal melanoma
  - Breast cancer
- Gaining traction in prostate cancer

Traditional Approaches to Staging Miss Patients with Aggressive Tumor Biology

Greater than 90% of patients
are considered lower risk
(Stage I and II) at the time of diagnosis



Because no two cancers are the same, many patients who have high-risk tumor biology are being **misidentified** as lower risk at the time of diagnosis

However, more than half of the deaths caused by melanoma (excluding Stage IV) occur in patients who were originally diagnosed as lower risk (Stage I or II)

AJCC staging, based on clinicopathologic features, alone is inadequate for predicting clinical outcomes

AJCCv7 *J Clin Oncol* 2009. SEER data release 2017

A more accurate prognosis and the resulting change in patient management, such as increased surveillance, have been shown to lead to earlier detection of recurrence and, in turn, improved outcomes

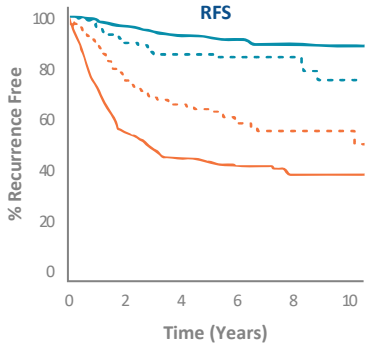
Kurley et al. European Association of Dermato Oncology (EADO) conference in Seville, Spain; April 21-23, 2022

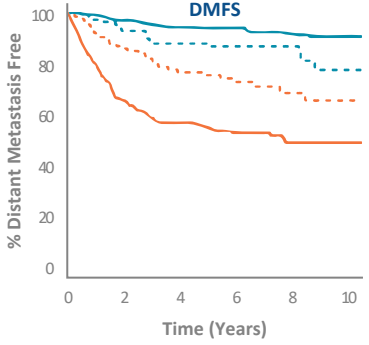
2X as likely to survive

Patients are twice as likely to survive if they have asymptomatic recurrence detected, compared to those who have symptoms at the time their recurrence is detected

Wong *Eur J Nucl Med Mol Imaging*, 2017

DecisionDx-Melanoma GEP Has Consistent and Independent Evidence of Prognostic Value across Studies





FEATURE	HR RFS (95% CI) p-value	HR DMFS (95% CI) p-value
Breslow thickness (per mm)	1.12 (1.03-1.22), p=0.01	1.14 (1.02-1.26), p=0.02
Ulceration	1.63 (1.18-2.25), p=0.003	2.03 (1.48-2.78), p<0.001
Age (per year)	1.01 (0.99-1.03), p=0.60	1.00 (0.98-1.03), p=0.65
SLNB	2.42 (1.88-3.10), p<0.001	2.80 (2.07-3.77), p<0.001
31-GEP test	**2.90 (2.01-4.19), p<0.001**	**2.75 (1.76-4.32), p<0.001**

DecisionDx-Melanoma

- Quantifies expression of 31 genes from primary tumor using RT-PCR
- Applies validated algorithm

Class 1A Lowest Risk

Class 1B/2A Increased Risk

Class 2B Highest Risk

31-GEP class result remains a consistent component of all DecisionDx-Melanoma reports

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Greenhaw et al. *JAAD* 2020

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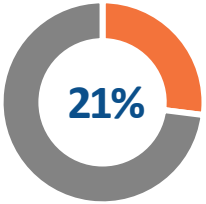
DecisionDx ▸Melanoma

Collaboration with the National Cancer Institute

Linking DecisionDx-Melanoma clinical testing with patients captured in the NCI-SEER Registry

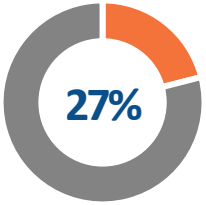
NCI/SEER Data Linked with DecisionDx-Melanoma Test Results

Data analysis of a cohort of real-world, unselected, prospectively tested patients with cutaneous melanoma



Benefit in Overall Survival (OS) in patients who were tested at 3 years over those who were not tested

	3-year OS (95% CI)	Deaths, % (n/N)
31-GEP Tested	93.1% (92.0-94.2%)	4.8% (174/3,621)
Matched Untested	91.2% (90.4-91.9%)	6.1% (658/10,863)
Hazard Ratio‡	**0.79 (0.67-0.93)**	**P=0.006**



Benefit in Melanoma Specific Survival (MSS) in patients who were tested at 3 years over those who were not tested

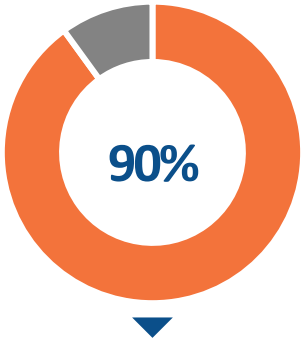
	3-year MSS (95% CI)	Deaths, % (n/N)
31-GEP Tested	97.7% (97-98.4%)	1.6% (58/3,621)
Matched Untested	96.6% (96.2-97.1%)	2.2% (238/10,863)
Hazard Ratio‡	**0.73 (0.54-0.97)**	**P=0.03**

Data provides direct evidence that patients tested with DecisionDx-Melanoma have better survival rates than untested patients and suggests that testing can aid in risk-aligned treatment plans for improved patient outcomes and survival rates

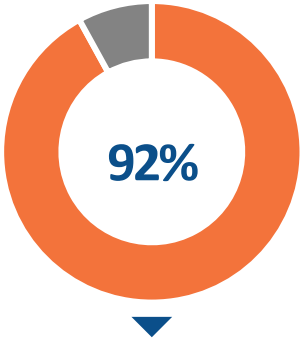
Kurley et al. Presented at European Association of Dermoto Oncology (EADO) conference in Seville, Spain; April 21-23, 2022

‡Hazard ratio (HR) was computed using the untested patients as referenced for 31-GEP tested cohort. A HR less than 1.0 demonstrates improved survival in 31-GEP tested patients. Diagnosis date 2016 and onward.

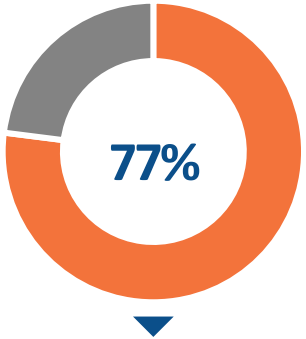
Patients with Melanoma Desire Testing with DecisionDx-Melanoma



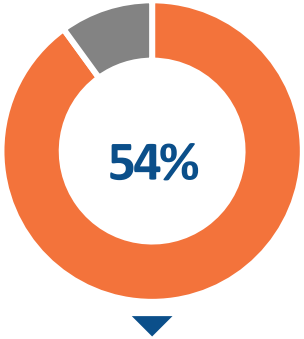
Wanted prognostic information about their melanoma tumors at diagnosis



Felt the testing was useful



Wanted testing to obtain all of the information they could about their melanoma



Of the patients who did not receive 31-GEP testing, 54% wished they had been offered the option

None of the patients surveyed indicated decision regret regarding their decision to obtain DecisionDx-Melanoma testing, even patients who received a poor prognosis/high-risk (Class 2) DecisionDx-Melanoma test result

Ahmed et al. *Cancer Medicine* 2022; some values have been rounded

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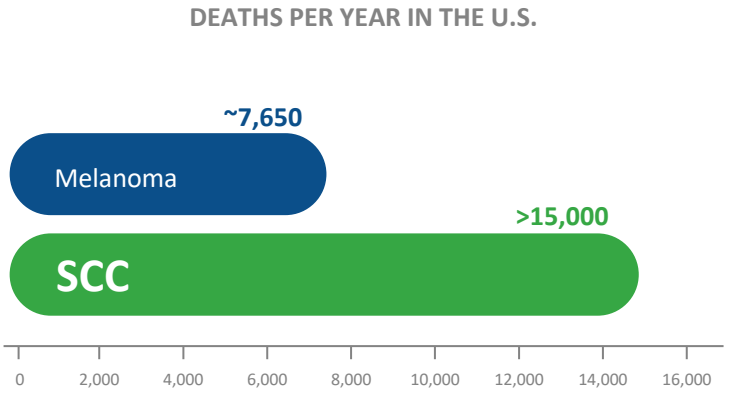
DecisionDx-SCC

Cutaneous Squamous Cell Carcinoma Is an Emerging Problem in the U.S.

- Managing SCC is a significant clinical issue as deaths from SCC are now estimated to exceed those from melanoma
- Because cancer treatment plans and their outcomes are guided by risk for metastasis, prognostic accuracy has direct implications on patient management
- Traditional staging fails to identify >30% of SCC cases who go on to metastasize, and >75% of SCC cases are over-called by staging
- Unlike melanoma, breast and other common cancers, SCC patient care has not been personalized with risk predicting gene expression profile (GEP) tests



Utility of traditional clinicopathologic risk factors is limited by their low positive predictive value

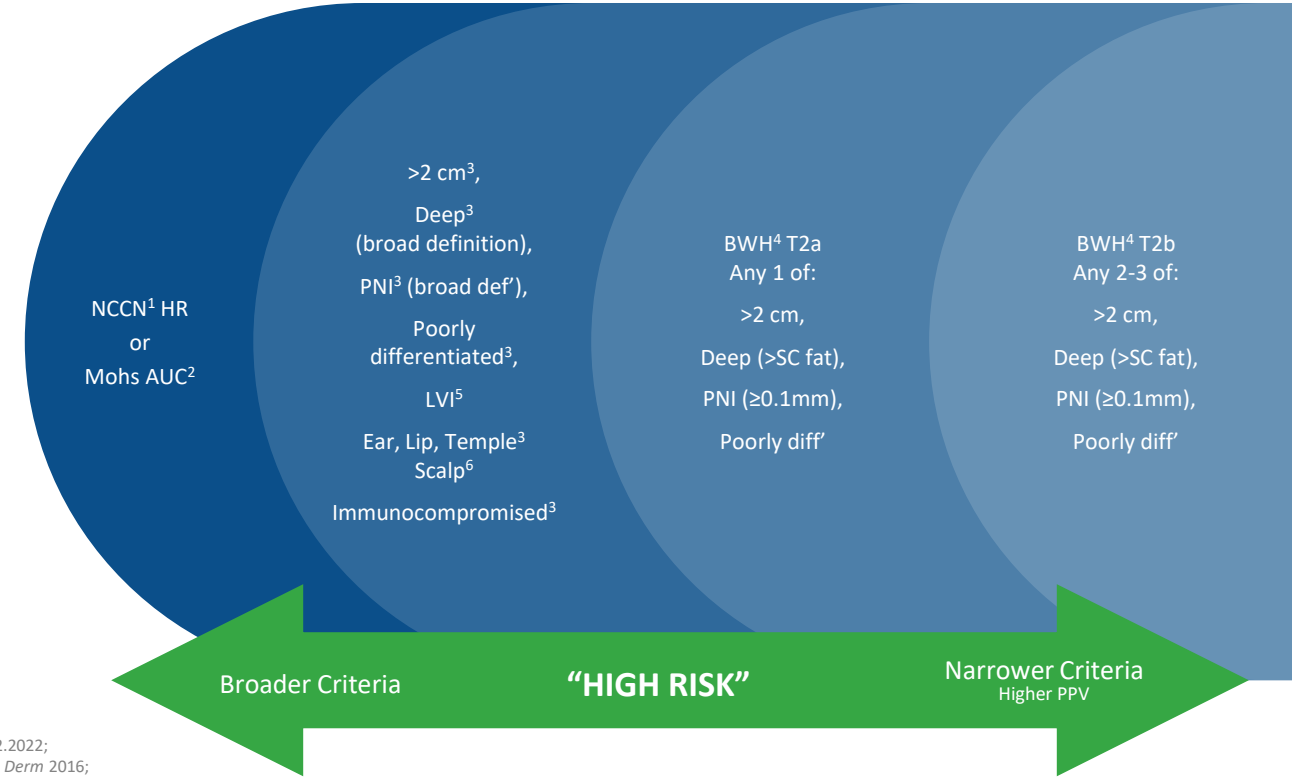
CASTLE BIOSCIENCES

SEER data release 2019; Mansouri et al. *JAMA Dermatol* 2017; https://www.skincancer.org/skin-cancer-information/skin-cancer-facts/

How is Risk Assessment Traditionally Done for SCC Patients?

The SCC community uses the term "high-risk" SCC to describe different patient populations

Additional Risk Factors from NCCN and Mohs AUC: Rapidly growing tumor, neurologic symptoms, LVI, site of prior RT or chronic inflammatory process, and select histologic subtypes (also see template for SCC testing criteria)



[1] NCCN Guidelines for Squamous Cell Skin Cancer v2.2022;
[2] Connolly et al. *JAAD* 2012; [3] Thompson et al. *JAMA Derm* 2016;
[4] Jambusaria-Pahlajani et al. *JAMA Derm* 2013;
[5] Skulsky et al. *Head & Neck* 2016; [6] Mo et al. *JAMA Derm* 2020

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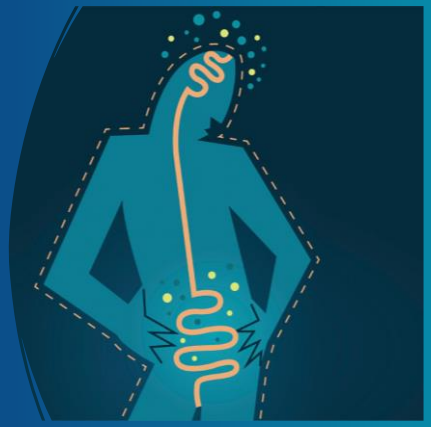
Current SCC Staging Options



- AJCC (American Joint Commission on Cancer)
- BWH (Brigham and Women's Hospital)
- NCCN (National Comprehensive Cancer Network)
- Gut Instinct

Staging Systems – Let's Dig a Little Deeper

Staging Systems – AJCC

Table 1. **Definitions for T, N, M**

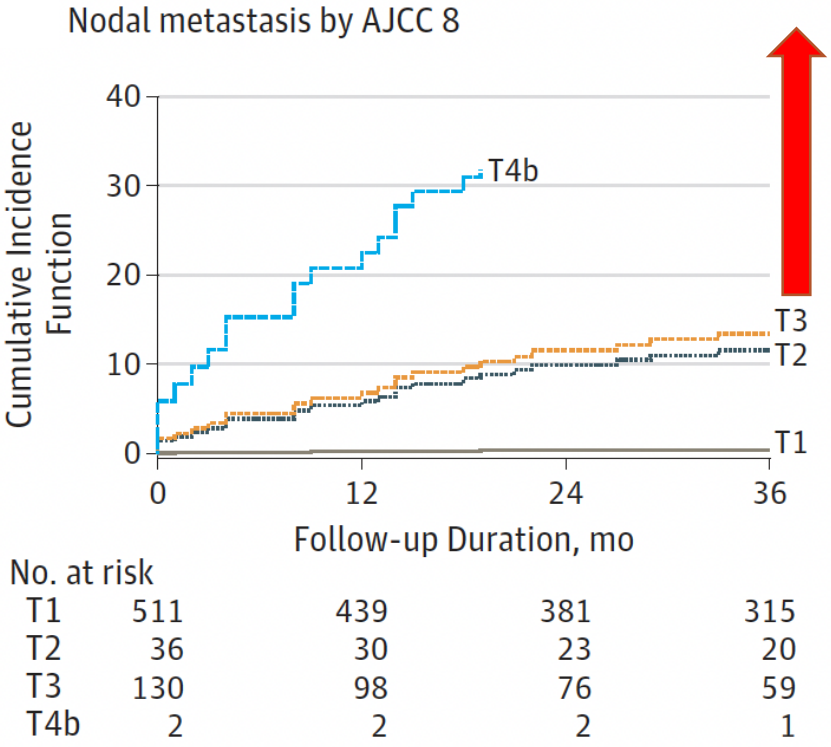
T	Primary Tumor
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor smaller than or equal to 2 cm in greatest dimension
T2	Tumor larger than 2 cm, but smaller than or equal to 4 cm in greatest dimension
T3	Tumor larger than 4 cm in maximum dimension or minor bone erosion or perineural invasion or deep invasion*
T4	Tumor with gross cortical bone/marrow, skull base invasion and/or skull base foramen invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement

*Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

Table 2. **AJCC Prognostic Stage Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	Any T	N3	M0
	T4	Any N	M0
	Any T	Any N	M1

AJCC Performance



Problem number 2

Problem number 1

JAMA Dermatol. 2019;155(7):819-825

Brigham and Women's Hospital System

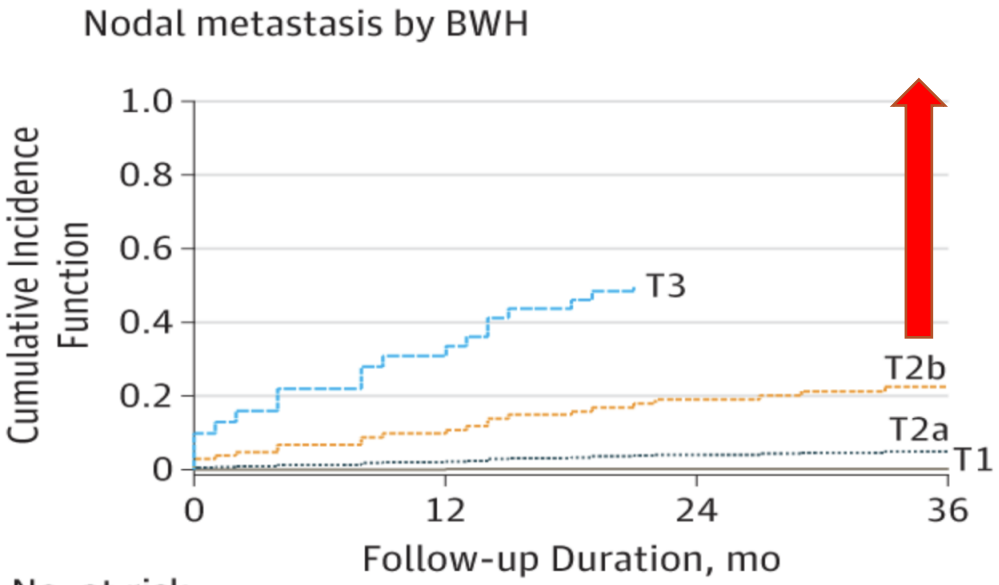
T1	0 risk factor
T2a	1 risk factor
T2b	**2–3 risk factors**
T3	**≥4 risk factors or bone invasion**

High-risk patients

Risk factors

- Tumor diameter ≥2 cm
- Tumor invasion beyond subcutaneous fat (excluding bone invasion, which automatically upgrades tumor to T3)
- Perineural invasion ≥0.1 mm
- Poorly differentiated

BWH Performance



No. at risk

T1	488	422	370	303
T2b	128	100	84	72
T2a	58	45	26	19
T3	5	3	2	1

Still a Problem

Better than AJCC

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JAMA Dermatol. 2019;155(7):819-825

NCCN Guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Squamous Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

STRATIFICATION TO DETERMINE TREATMENT OPTIONS AND FOLLOW-UP FOR LOCAL CSCC BASED ON RISK FACTORS FOR LOCAL RECURRENCE, METASTASES, OR DEATH FROM DISEASE

Risk Group[1]	Low Risk	High Risk	Very High Risk
Treatment options	See SCC-2	See SCC-3	See SCC-3
H&P			
Location/size[2]	Trunk, extremities ≤2 cm	Trunk, extremities >2 cm – ≤4 cm	>4 cm (any location)
		Head, neck, hands, feet, pretibia, and anogenital (any size)[5]	
Borders	Well-defined	Poorly defined	
Primary vs. recurrent	Primary	Recurrent	
Immunosuppression	(-)	(+)	
Site of prior RT or chronic inflammatory process	(-)	(+)	
Rapidly growing tumor	(-)	(+)	
Neurologic symptoms	(-)	(+)	
Pathology (See SCC-A)			
Degree of differentiation	Well or moderately differentiated		Poor differentiation
Histologic features: Acantholytic (adenoid), adenosquamous (showing mucin production), or metaplastic (carcinosarcomatous) subtypes	(-)	(+)	Desmoplastic SCC
Depth[3,4]: Thickness or level of invasion	≤6 mm and no invasion beyond subcutaneous fat		>6 mm or invasion beyond subcutaneous fat
Perineural involvement	(-)	(+)	Tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm
Lymphatic or vascular involvement	(-)	(-)	(+)

SCC Staging Challenges

Possible Solutions

- Clinically observe everybody (undertreat to avoid excess therapy)
- Treat everybody (overtreat)
- Refine our prognostic ability

DecisionDx-SCC Clinical Validity

- DecisionDx-SCC (40-GEP) predicts metastatic risk for SCC patients with one or more risk factors
- DecisionDx-SCC accurately classifies patients as low, moderate or high biological risk (Class 1, Class 2A, Class 2B)
- DecisionDx-SCC is supported by 11 peer-reviewed publications demonstrating both clinical validity and clinical utility, and >70% of these publications have occurred in 2021 and 2022, highlighting the rapidly growing body of evidence since the launch of the test on September 2, 2020
- DecisionDx-SCC is an accurate and independent predictor of SCC metastasis in univariate and multivariate analyses against traditional prognostic risk factors such as perineural invasion, deep invasion and poor differentiation
- Class 1 patients have a <7% risk of metastasis, Class 2A patients a 20% risk of metastasis and Class 2B patients a >50% risk of metastasis

DecisionDx-SCC Clinical Utility

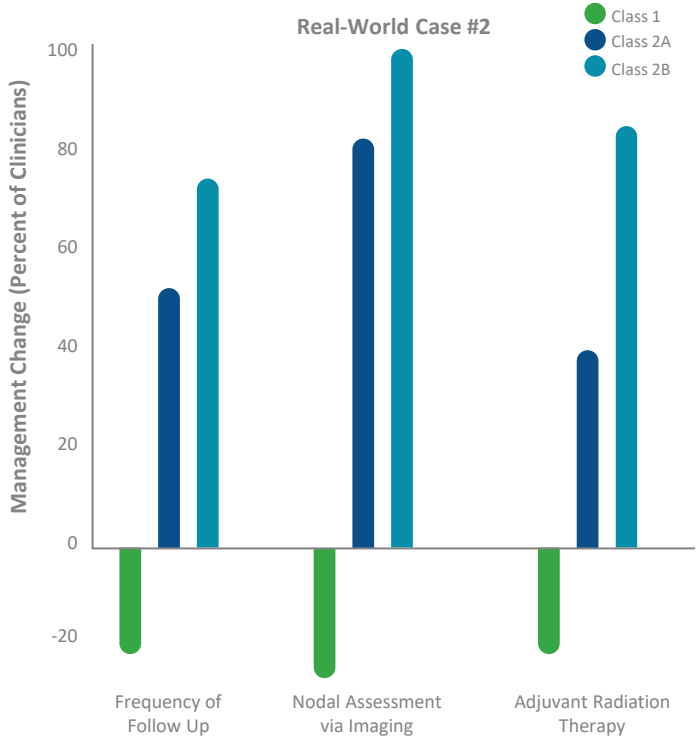
- DecisionDx-SCC has published clinical utility and clinical impact studies with over 600 clinicians and 300 patients
- Risk-aligned management changes include frequency of clinical visits/follow-up, baseline and surveillance nodal imaging decisions, referrals and sentinel lymph node biopsy (SLNB) decision making, and adjuvant therapy decisions (radiation therapy, systemic therapy)
- DecisionDx-SCC delivers actionable results across the risk spectrum, whether considering the number of high-risk factors a patient has or how they are staged using BWH or AJCC8
- DecisionDx-SCC results can inform management decisions within established guidelines (e.g., NCCN); driving treatment plans from low to moderate to high intensity management

DecisionDx-SCC Real-World Use

- Real-world use data indicates that DecisionDx-SCC is being ordered for the intended use population; high-risk SCC patients with one or more risk factors
- In the first year of clinical testing, >75% of patients tested had two or more high risk factors with an average of 2.8
- Greater than 99% of those patients were either high risk or very high risk by NCCN guidelines

Adapted from Farberg et al. Presented at Winter Clinical Dermatology, January 14-19, 2022

DecisionDx-SCC Impacts Management Planning by Real-World Test Users for Real-World Patients



Age:	69
Sex:	Female
Location:	R inferior postauricular skin
Subtype:	Infiltrating
Differentiation:	Moderate Additional
High-Risk Factors:	N/A
Total Risk Factors:	1 risk factor

A Class 2B result changed over ~70% of clinician management plans to increase follow-up frequency, and consider or recommend nodal imaging and adjuvant radiation therapy

A Class 2A result changed ~40-80% of clinician management plans to increase follow-up frequency, and consider or recommend nodal imaging and adjuvant radiation therapy

Hooper et al. *Cancer Investigation* 2022 (In Press)

CASTLE BIOSCIENCES

Matthew Goldberg, M.D., F.A.A.D.

MyPath | DiffDx Melanoma

Inflammatory Skin Disease Pipeline Program

Unmet Need in Patients with a Difficult-to-Diagnose Pigmented Lesion

The Clinical Problem

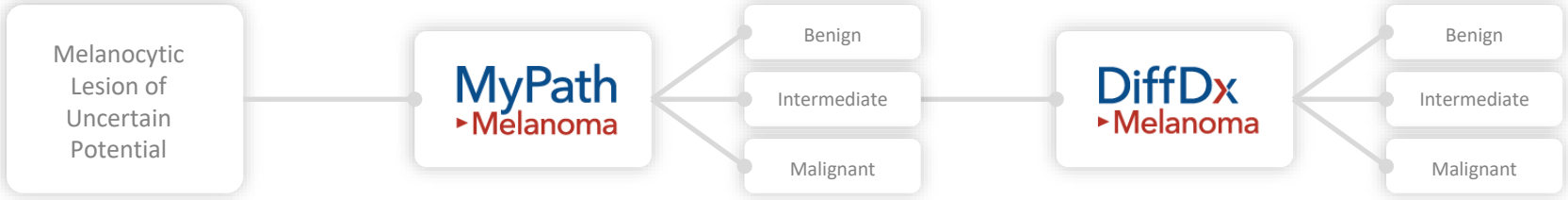
A clinical hurdle for dermatopathology is the accurate diagnosis of difficult-to-diagnose melanocytic neoplasms

Of the estimated two million suspicious pigmented lesions biopsied annually in the U.S., approximately 300,000 of those cannot be classified with confidence as either benign tissue or melanoma through traditional histopathology methods

These difficult-to-diagnose lesions are commonly sent for second opinions to expert dermatopathologists who have more experience with challenging cases; however, the nature of many lesions remains ambiguous with discordant rates of lesions in this category of 25-43% (Elmore et al. 2017)

Diagnostic ambiguity can lead to clinical management uncertainty and overtreatment, leading to unnecessary excisions and increased patient morbidity, and undertreatment, with the potential for missing diagnoses of malignant melanoma

MyPath Melanoma and DiffDx-Melanoma Are Validated to Classify Ambiguous Melanocytic Lesions as Suggestive of Benign or Suggestive of Malignant



MyPath | DiffDx ▸Melanoma

- Leverages the strengths of two validated GEP tests to help guide better patient care
- Utilizes power of clinical evidence and peer-reviewed publications
- Shown to reduce rate of non-actionable (intermediate or technical failure) results to 1.3%[1]

MyPath Melanoma

- Quantifies expression of 23 genes including two variants of PRAME
- Over 35,000 lesions tested in the clinical setting
- Validated in over 1,300 melanocytic neoplasms
- Can be used in pediatric patients
- Measured an 80% reduction in excisions with benign test results

DiffDx-Melanoma

- Quantifies expression of 35 genes
- Provides additional information when the MyPath Melanoma result is intermediate*
- Uses neural networks – an artificial intelligence approach to machine learning for model development
- Validated on a wide variety of subtypes
- Low rate of intermediate cases

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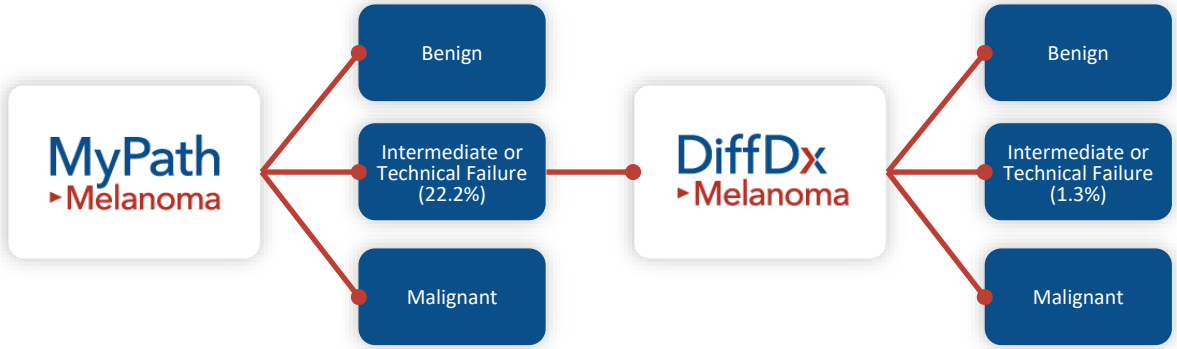
*DiffDx-Melanoma will only be performed on MyPath intermediate cases of patients 18 years or older

[1]Goldberg et al. *SKIN* 2021: s79

Diagnostic GEP is Designed to Provide Clinically Actionable, Objective Results for Nearly All Patients



>98%

By leveraging our second GEP test, >98% of patients with ambiguous melanocytic lesions received a clinically actionable result[1]

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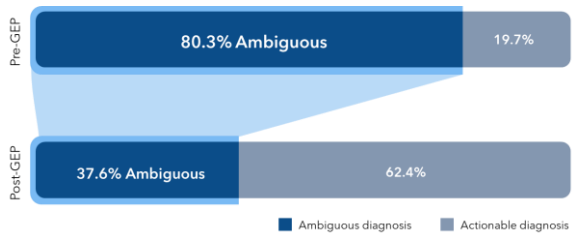
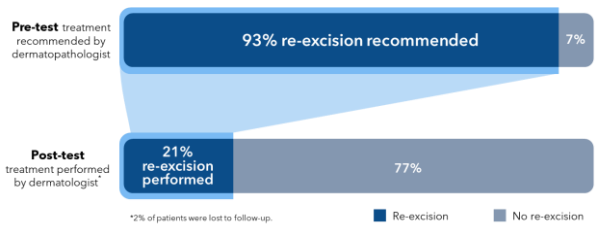
[1]Goldberg et al. *SKIN* 2021: s79

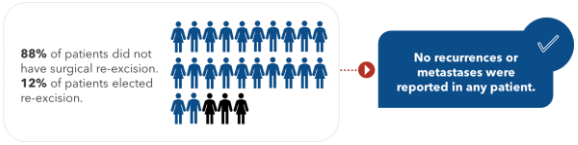
Diagnostic GEP Has Clinical Utility for Dermatopathologists and Dermatologists



Reduced rate of indeterminate diagnoses by dermatopathologist[1]



Fewer re-excisions in benign lesions by dermatologists[2]



No adverse events for patients with benign GEP results and no surgical intervention[4]

Multiple peer-reviewed publications show clinical utility of GEP in ambiguous melanocytic lesions for dermatopathologists and dermatologists for the benefit of patient care[1-4]

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[1]Cockerell, et. al. 2016; [2]Cockerell, et. al. 2017; [3]Farberg, et. al. 2020; [4]Tschen, et. al. 2021

Case Study: High Clinical Suspicion for Melanoma

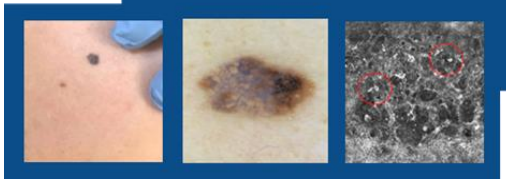
A 27-year-old female patient was seen by a primary care physician who recommended follow-up with a dermatologist for assessment of a concerning melanocytic lesion. Patient has a family history of melanoma and pancreatic cancer.

Clinical Description

- Asymmetrical lesion, 6 mm in diameter on back
- Blue color and round structures visualized by dermoscopy and confocal microscopy

Clinical Differential Diagnosis

- Melanoma in-situ
- Malignant melanoma
- Regression of atypical nevus

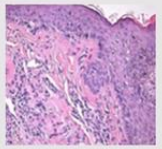


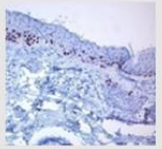
Histopathological Findings

It was noted in the pathology report that there were suspicious, atypical findings including focal confluence of nests, areas of irregular epidermal distribution, and dense inflammation.

Diagnosis and Recommendation Prior to Testing

A final diagnosis of melanocytic nevus, compound type, with atypical features, dense inflammation, and fibrosis was rendered by the dermatopathologist with recommendation for clinical follow-up.





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Case contributed by: Dermatologist, Portland, OR

Case Study: High Clinical Suspicion for Melanoma (cont.)

Due to the conflicting histopathological and clinical features, the optimal treatment plan was unclear and MyPath Melanoma testing was ordered by the dermatologist.

Test Result

MyPath Melanoma resulted in a gene expression profile:

Suggestive of Malignant Neoplasm

Impact to Patient Care

Following the MyPath Melanoma test result, the treatment plan was modified to include re-excision and quarterly follow-up. An addendum to the pathology report was issued noting that while not definitive, the histopathological findings could not exclude melanoma in-situ arising within a nevus.

A follow-up skin check at four months revealed an additional melanoma and two evolving pigmented nevi under close monitoring with dermoscopy.

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Case contributed by: Dermatologist, Portland, OR

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Inflammatory Skin Disease

Pipeline test to predict response to systemic therapies with target launch by 2025

Targeting the Unmet Need in Moderate-to-Severe Psoriasis and Atopic Dermatitis

Common skin diseases with significant patient impacts and costs to health care system

- Psoriasis (PSO) and Atopic Dermatitis (AD) are among the most frequently seen skin rashes
- Treatments are significantly different for PSO and AD and can be costly (e.g., Humira for PSO ~$68k/year; Dupixent for AD is ~$38k/year)
- Cutaneous T Cell Lymphoma (CTCL) can mimic clinical presentation of AD and PSO
- Systemic therapies are currently prescribed using a trial-and-error approach
- **Systemic therapy guidance tools have the potential to streamline therapeutic interventions for patients and avoid ineffective, expensive medication courses**

Inflammatory Skin Disease Treatment Patient Journey Using Standard Clinical Practice

1. Patient presents with skin signs and symptoms to provider
2. Clinical diagnosis of psoriasis, atopic dermatitis or related condition is made
3. Typically, topical treatment is initiated, while some proceed directly to systemic therapy based on disease severity
4. Depending on initial treatment efficacy or disease severity, systemic treatment is considered
5. Management plan determined based on clinical features and response to therapy
6. Patient begins new systemic therapy

Trial and error treatment loop

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Castle Has Started Two Studies to Aid in Treatment of Inflammatory Skin Diseases

IDENTITY

- Help guide therapy selection for atopic dermatitis and psoriasis
- Prospectively enrolling, multi-center study
- Sample obtained through non-invasive skin scraping sample collection method

SIGNAL-MF

- Identify mycosis fungoides (MF)[1] – a type of cutaneous T-cell lymphoma that can mimic atopic dermatitis or psoriasis
- Sample obtained through non-invasive skin scraping sample collection method
- Prospectively enrolling, multi-center study
- Targeting 15 sites for enrollment; 13 committed[2]

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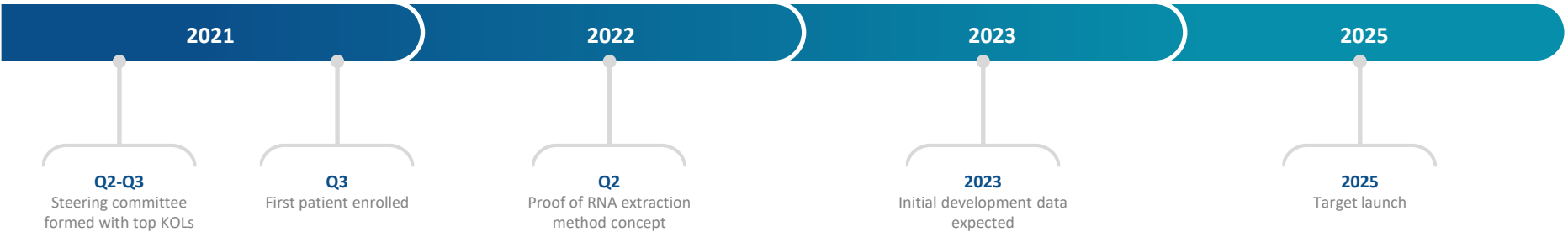
[1]For MF, the most common type of CTCL, the incidence is ~1,600 new cases per year (as of 2016) according to Teras et al, CA, 2016; [2]Data as of 9/08/22

IDENTITY Study

Castle's inflammatory skin disease pipeline test is being developed to predict systemic therapy response

55
Committed Sites

337
Patients Enrolled[1]

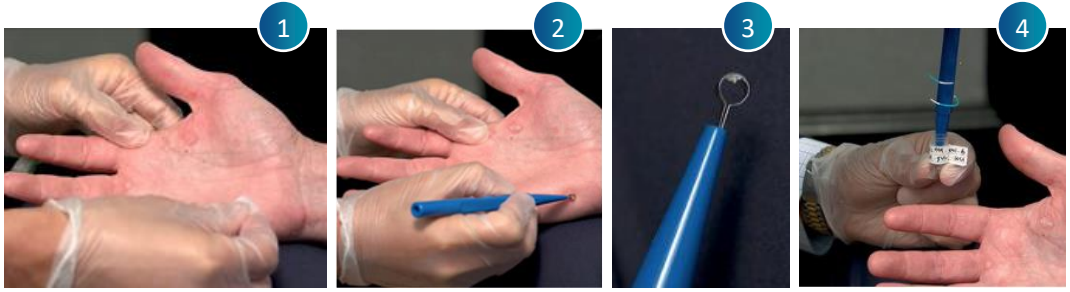


Program Milestones

Data as of 9/08/22; [1]patients with moderate-to-severe disease

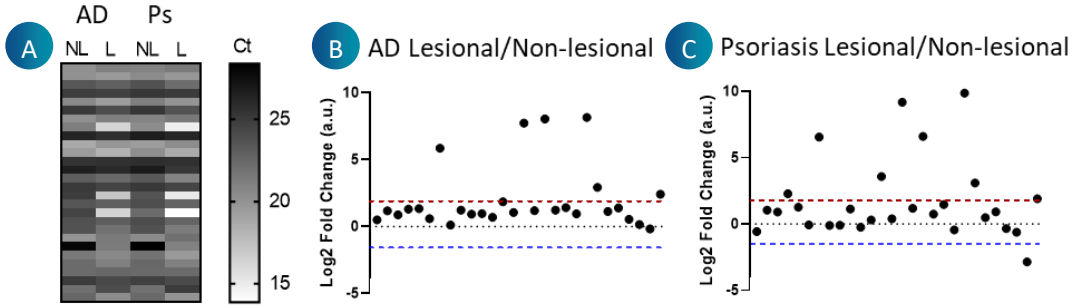
The Non-Biopsy Tissue Collection Method for Our Inflammatory Skin Disease Pipeline Test Has Been Validated

Scraping technique to collect superficial epidermis samples



Skin prep-cleaning with alcohol swab | Gentle scraping with a curette | Quality check | Storage in RNA preserving buffer

Gene expression patterns in atopic dermatitis and psoriasis



Raw Ct values of genes assessed for non-lesional (NL) and lesional (L) skin samples from patients with atopic dermatitis (AD) and psoriasis (P)

Change above the red line indicates an increase in gene expression and below the blue line indicates a decrease in gene expression

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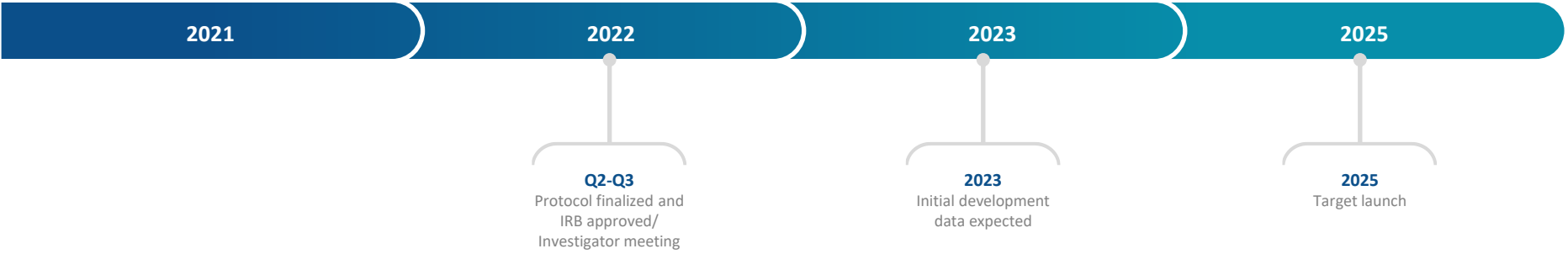
Quick et al. 4th Annual Revolutionizing Atopic Dermatitis (RAD) Conference in Baltimore; April 9-11, 2022

SIGNAL-MF Study

Castle's Inflammatory Skin Disease pipeline test could include an ancillary diagnostic to identify mycosis fungoides

15
Target Sites

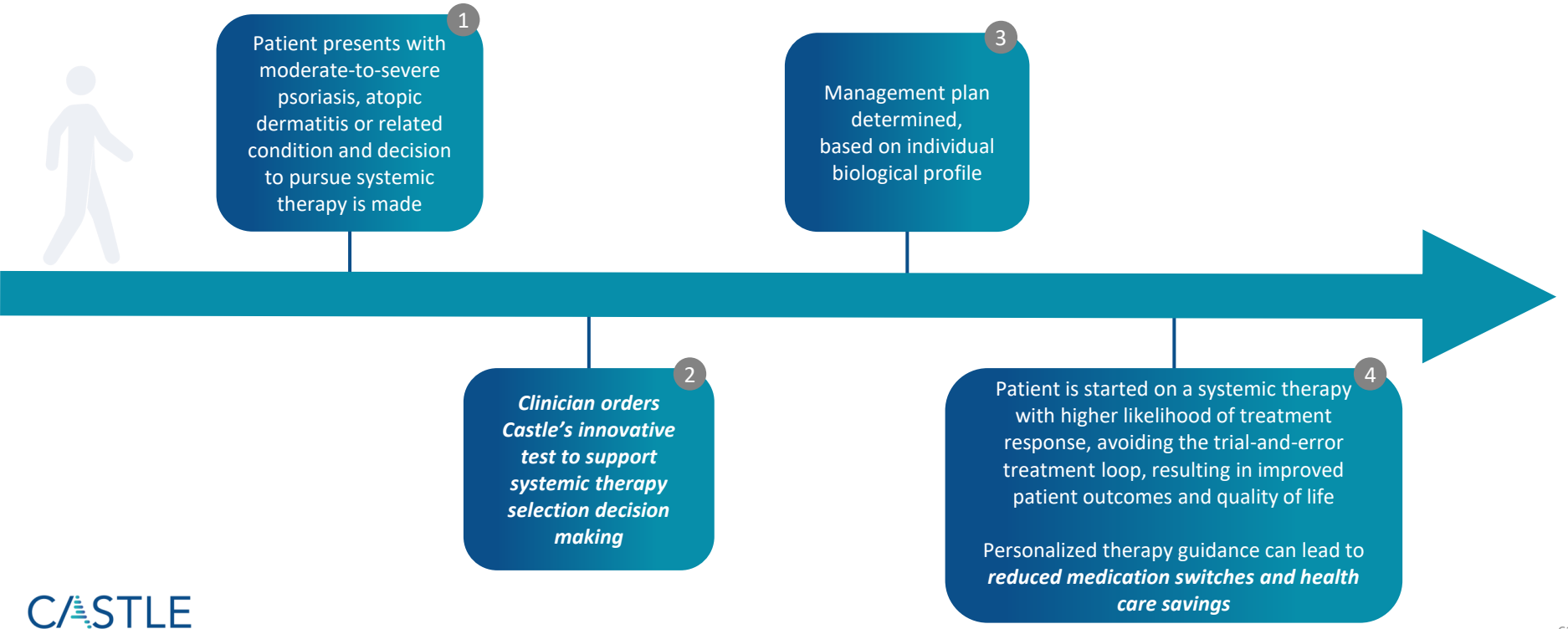
500
Target Patient Enrollment



Program Milestones

Our Test is Expected to Predict Response to Systemic Therapies for Patients with Moderate-to-Severe Psoriasis, Atopic Dermatitis and Other Related Diseases

Our test is expected to be launched in phases, starting with systemic therapies most commonly prescribed in the IDENTITY study cohort



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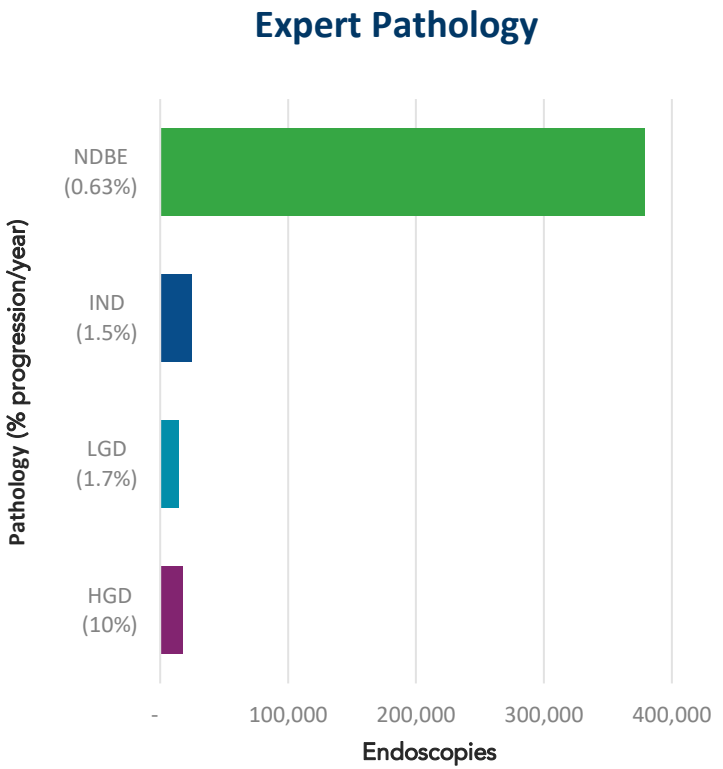
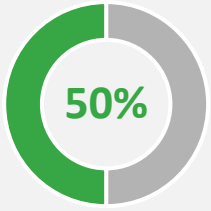
Craig Munroe, M.D.

TissueCypher
Barrett's Esophagus

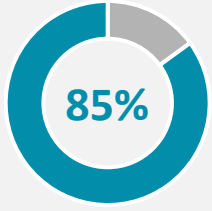
435,000 Barrett's Esophagus Related Endoscopies Per Year



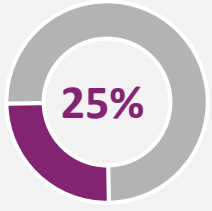
Need for additional risk stratification tools



50% of annual progressors are initially diagnosed as non-dysplastic[1]



Up to 85% of low-grade patients are downgraded upon expert GI pathology review[2,3]



25% of high-grade/cancer diagnoses occur within 1 year of endoscopy[4]

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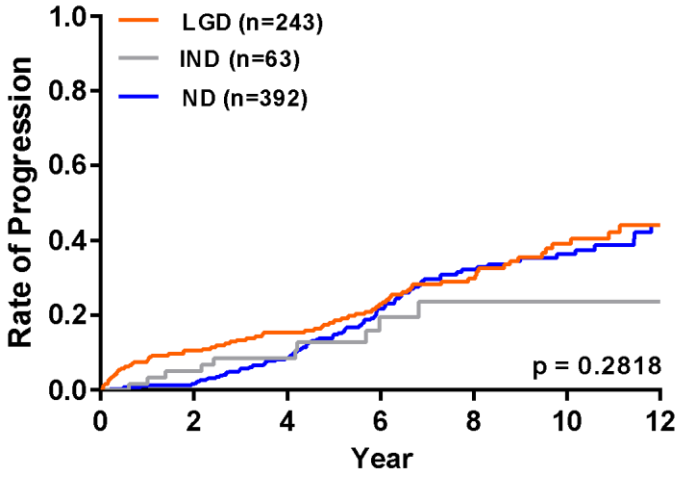
NDBE=Non-dysplastic Barrett's esophagus; IND=indefinite for dysplasia; LGD=low-grade dysplasia; HGD=high-grade dysplasia

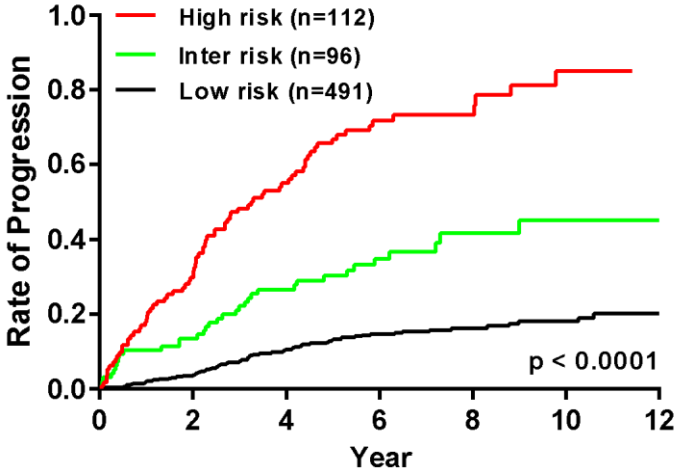
[1]Progression rates: Rastogi et al. *Gastrointest Endosc* 2008; Krisnamoorthi et al. *Gastrointest Endosc* 2020; Singh et al. *Gastrointest Endosc* 2014; Wani et al. *Clin Gastroenterol Hepatol* 2011; [2]Curvers et al. *Am J Gastroenterol* 2010; [3]Duits et al. *Gut* 2015; [4]Visrodia et al. *Gastroenterology* 2016.

TissueCypher Is the Strongest Independent Predictor of Progression

Original Pathologic Diagnosis



TissueCypher



HR = 7.7 (high- vs. low-risk) p<0.0001

HR = 2.8 (inter- vs. low-risk) p<0.0001

n=699 patients[1-5] (ND n=567, IND n=50, LGD n=82)
152 incident progressors, 38 prevalent cases, 509 non-progressors

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HR = Hazard ratio. Pooled analysis completed by Castle Biosciences. [1]Critchley-Thorne et al. *Cancer Epidemiol Biomarkers Prev* 2016; [2]Critchley-Thorne et al. *Cancer Epidemiol Biomarkers Prev* 2017; [3]Davison et al. *Am J Gastroenterol* 2020; [4]Frei et. al. *Clin Transl Gastroenterol* 2020; 5 Frei et. al. *Am J Gastroenterol* 2021

AFTER RECEIVING A HIGH-RISK SCORE…

- NDBE patients are at 18-fold higher risk of progression[1]
- LGD patients are at 6.7-fold higher risk of progression[2]
- Patients harboring prevalent disease are 46 times more likely to return a high-risk score[3]
- 9.4 times more likely to progress within 1–5 years[4]

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[1]Iyer et al. *Clin Gastroenterol Hepatol* March 2022; [2]Frei et. al. *Am J Gastroenterol* 2021; [3]Critchley-Thorne et al. *Cancer Epidemiol Biomarkers Prev* 2017; [4]Critchley-Thorne et al. *Cancer Epidemiol Biomarkers Prev* 2016.

AFTER RECEIVING A LOW-RISK SCORE…

- NDBE patients are 3.2x less likely to progress vs histologic assessment[1]
- LGD or IND patients are 2.5x less likely to progress vs histologic assessment[1]

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[1]Data on file, Castle Biosciences

2022 American Gastroenterological Association (AGA) Clinical Practice Update

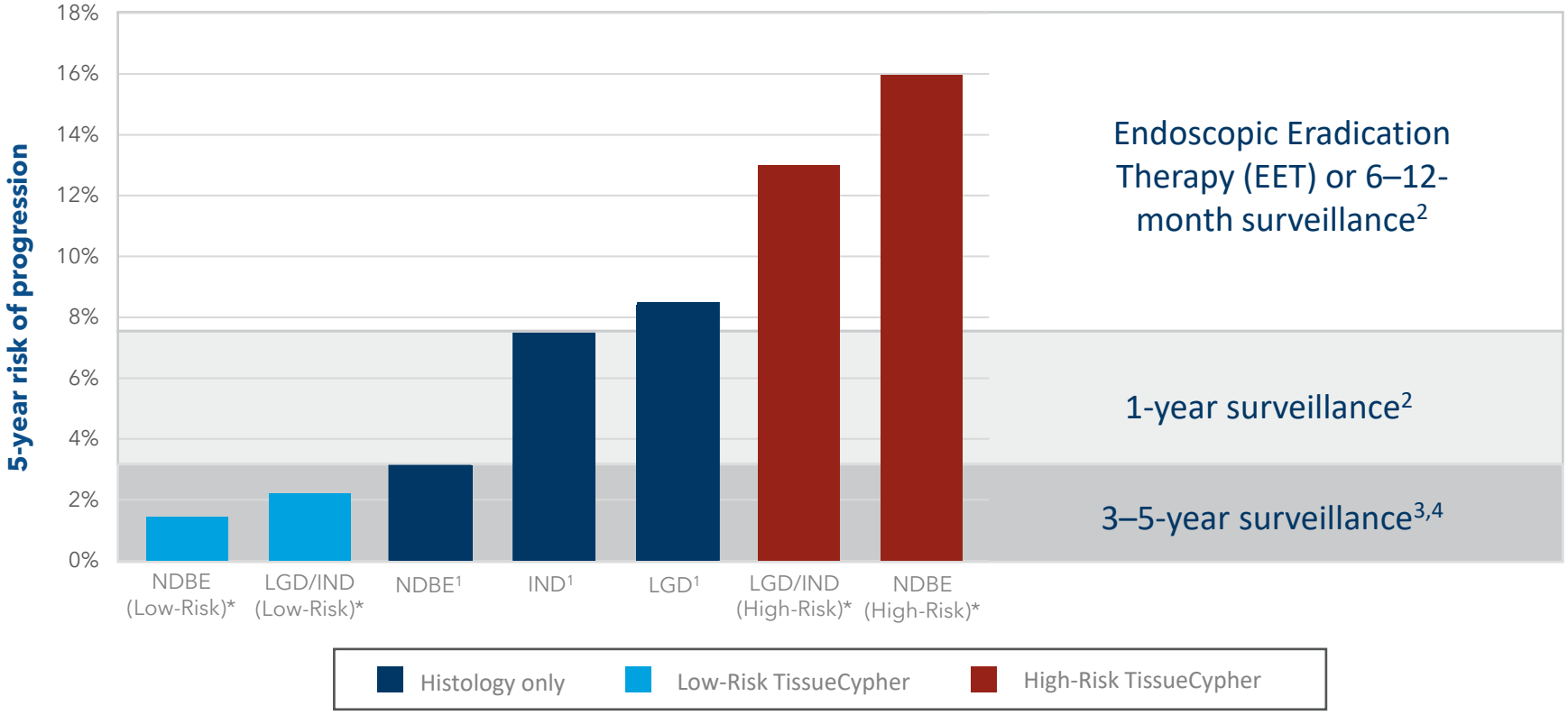
New Technology and Innovation for Surveillance and Screening in Barrett's Esophagus: Expert Review

V. **Raman Muthusamy**, M.D., MAS, **Sachin Wani**, M.D., C. **Prakash Gyawali**, M.D., **Srinadh Komanduri**, M.D., MS, for the CGIT Barrett's Esophagus Consensus Conference Participants

- **Best Practice Advice Statement #9:** Tissue systems pathology-based prediction assay [TissueCypher] may be utilized for risk-stratification of patients with non-dysplastic BE
- **Cited Evidence:** A high-risk score in non-dysplastic BE patients was associated with a rate of progression of 6.9%, similar to LGD
- **Care Pathway:** The CPU incorporates TissueCypher into a proposed BE care pathway to enable clinicians to use TissueCypher for risk stratification of new NDBE patients and NDBE patients under surveillance

Komanduri et al. *Clin Gastroenterol Hepatol* 2022

Consideration of Patient Management Based on Risk of Progression



[1]Progression rates: Rastogi et al. *Gastrointest Endosc* 2008; Krisnamoorthi et al. *Gastrointest Endosc* 2020; Singh et al. *Gastrointest Endosc* 2014; Wani et al. Clin *Gastroenterol Hepatol* 2011. [2]Consensus guidelines from ACG (2015), AGA (Medical Position Statement, 2011) and ASGE (2019); [3]Shaheen et al. Am J *Gastroenterol* 2022 [4]Komanduri et al. *Clin Gastroenterol Hepatol* 2022. *Data on file, Castle Biosciences. Data from pooled analysis of TissueCypher's risk stratification performance reported in five clinical validation studies.

How Incorporation of TissueCypher Testing Can Change Clinical Practice

Clinical guideline based on histology and segment length

NDBE	IND	LGD
Surveillance in 3 to 5 years[1,2,3] 3 years if segment length ≥3 cm^2 5 years if segment length < 3 cm^2	Surveillance in 3 to 6 months following PPI Rx, Surveillance in 12 months for persistent IND[1,2]	EET or Surveillance in 6-12 months[1,2]

TissueCypher
▸Barrett's Esophagus

LOW Risk Class

NDBE	IND/LGD BE
Consider surveillance in 3 to 5 years	Consider surveillance in 12 months and PPIs as needed

HIGH/INT Risk Class

NDBE	IND/LGD BE
Rule out prevalent HGD/EAC and consider EET or surveillance in 1 year	Rule out prevalent HGD/EAC and consider EET and PPIs as needed

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EET = Endoscopic Eradication Therapy; PPI = Proton pump inhibitor
[1]Consensus guidelines from ACG (2015), AGA (Medical Position Statement, 2011) and ASGE (2019); [2]Shaheen et al. *Am J Gastroenterol* 2022; [3]Komanduri et al. *Clin Gastroenterol Hepatol* 2022

Dr. Srinadh Komanduri Video

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Robert Cook, Ph.D.

IDgenetix

The Mental Health Community Expects More Personalized Care

Right Rx the First Time

Faster Rx Response and Remission

Reduction in Side Effects

Reduction in Personal Healthcare Costs

Medication Selection for Mental Illness Is Challenging

Inadequate Therapy Response

~53% of patients with major depressive disorder (MDD) have an inadequate response to first-line treatment[1]

Low Remission Rates

72% of patients with MDD do not achieve remission using current standard of care treatment approaches[2]

High Prevalence of Adverse Drug Events

The likelihood of discontinuation rises from 8.6% with first-line medication treatment to 41.4% with fourth-line treatment[3]

"…finding an effective antidepressant can take years"
- Mental Health America

[1]https://pubmed.ncbi.nlm.nih.gov/16390886/; [2]https://pubmed.ncbi.nlm.nih.gov/16390886/
[3]STAR*D Trial Combined Across Four Medication Cycles

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
- >2.5x improved chance of remission of depression symptoms

Easy to Use

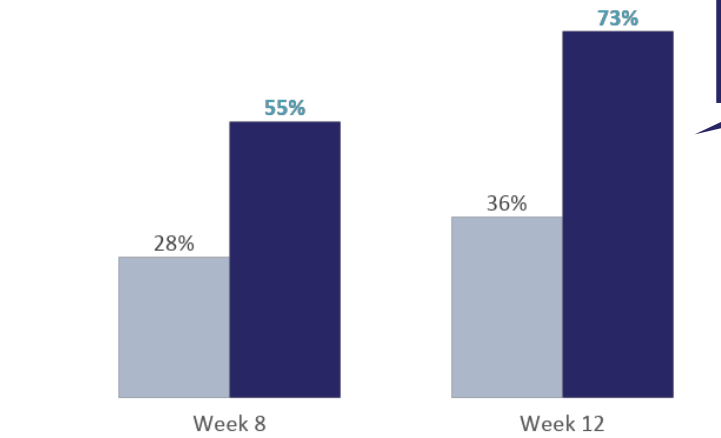
- 10 mental health and pain conditions in one report
- <1 minute to collect DNA sample
- 3-5 days to receive test report
- Specialized sales and medical science liaison support

Bradley et al. *J Psychiatr Res* 2018.

2.5x Increase in Remission Rates for Severe Depression Demonstrated Enhanced Clinical Outcomes vs. Standard of Care

Response Rate

≥ 50% Reduction from Baseline



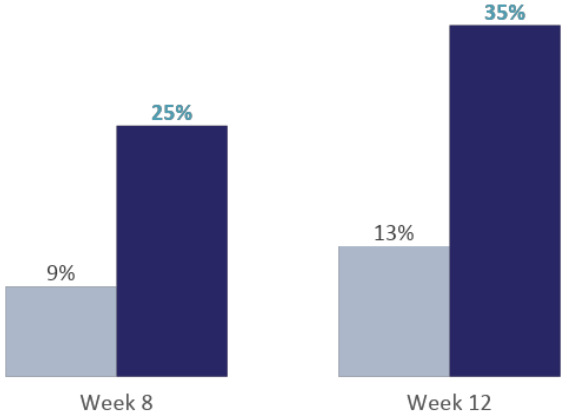
2x
increase in response rate vs. control

p-value	*0.01*	*0.001*

Remission Rate

Patients Achieving Remission

>2.5x
increase in remission rate vs. control



p-value	*0.05*	*0.02*

Control
IDgenetix

Bradley et al. *J Psychiatr Res* 2018.

Why IDgenetix PGx Is Important

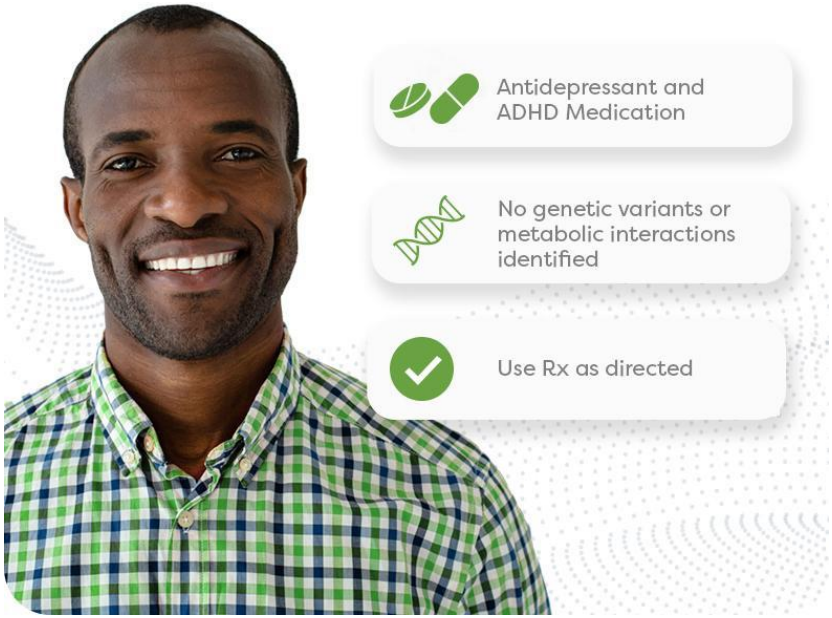
IDgenetix is redefining the standards of next generation PGx

	IDgenetix	PGx Original	Trial & Error
Multi-Gene Test	✓	✓	
RCT/Clinical Utility	✓	✓	
Medicare Coverage	✓	✓	
Comorbidity (MDD & Anxiety)	✓		
Drug-Drug Interactions	✓		
Lifestyle Factors	✓		

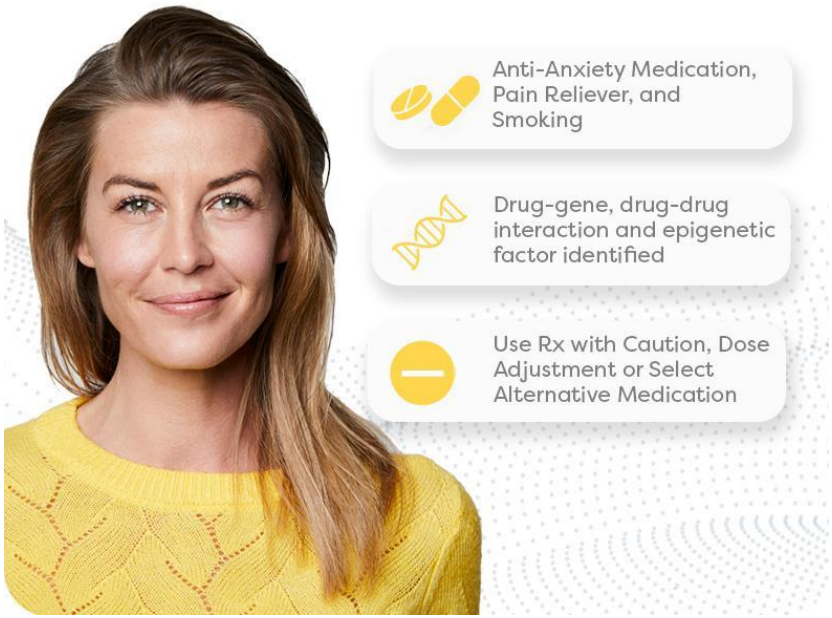
IDgenetix Addresses an Important Clinical Question:

How do providers personalize medication choices to increase chances of response and/or remission?

USE AS DIRECTED



USE WITH CAUTION



IDgenetix: Next Generation Precision Medicine

Old World

- Trial and error
- No genetic testing

New World

- Actionable report with clinical support
- Proprietary bioinformatics platform
- Randomized controlled trials

Integrated Bioinformatics Platform

Age & Metabolism

Drug-Gene Interactions

Drug-Drug Interactions

Lifestyle Factors & Environment

The future of mental health treatment is expected to include PGx as a fundamental part of everyday, best practice medical care

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Frank Stokes

ESG Overview

Financial Overview

Our Culture and Operations Were Built on ESG Principles

Helps mitigate risks and create opportunities

Helps progress our vision to transform disease management by keeping people first: patients, clinicians, employees and investors

Builds employee engagement and retention

Uncovers potential financial opportunities

Advances sustainable long-term value creation for our stockholders

Review and oversight of our ESG program resides with the Audit Committee of the Board

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ESG Focus Areas for 2022 and Beyond

Corporate ESG Performance
RATED BY ISS ESG
Prime

MSCI ESG RATINGS
AA
CCC | B | BB | BBB | A | AA | AAA


Environmental policy


Environmental metrics


DEI statement


DEI metrics


DEI action plan/roadmap


Vendor code of conduct/supplier standard

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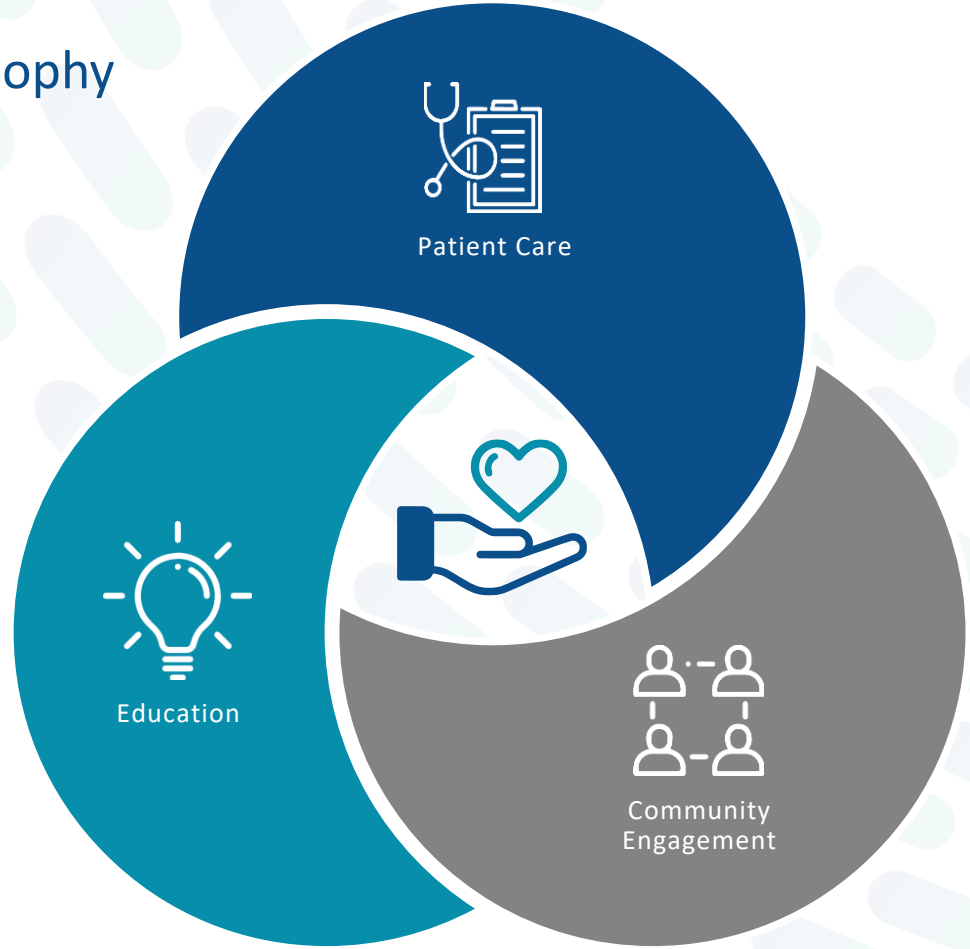
In 2022, Castle Biosciences received a rating of AA (on a scale of AAA-CCC) in the MSCI ESG Ratings assessment.

Our Giving Philosophy



Financial Overview

Our Financial Focus

- Drive Robust Test Volume Growth
- Maintain Industry-Leading Adjusted Gross Margins
- Achieve Operating Cash Flow Positivity by 2025
- Maintain Strong Balance Sheet
- Follow Disciplined Capital Allocation

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Financial Performance Summary Q2 2022

	2Q21	2Q22	Six Months Ended June 30, 2022
Total test reports	7,007	**11,034**	**19,661**
Total Derm test reports	6,539	**9,424**	**17,539**
Revenue	$22.8M	**$34.8M**	**$61.7M**
Adj. Revenue[1]	$22.9M	**$34.3M**	**$62.0M**
Gross Margin	82.6%	**71.9%**	**71.8%**
Adj. Gross Margin[1]	83.9%	**77.6%**	**78.0%**
Operating Cash Flow	$(6.4)M	**$(9.0)M**	**$(30.4)M**
Adj. Operating Cash Flow	$(4.3)M	**$(9.0)M**	**$(30.4)M**
Cash & Cash Equivalents as of 06/30/2021	$368M	**$273M**	**$273M**

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[1]See Non-GAAP reconciliations at the end of this presentation.

Committed to Delivering Long-term Growth with Net Operating Cash Flow Positivity by 2025

	Three-year plan (2025)
Revenue	25-35% year-over-year growth[1]; Total revenue in 2025 of $255m-$330m
Adjusted Gross Margins	80%-85% by 2025
Other Operating Expenses[2]	75%-85% of revenue by 2025
Net Operating Cash Flow	Positive[3]

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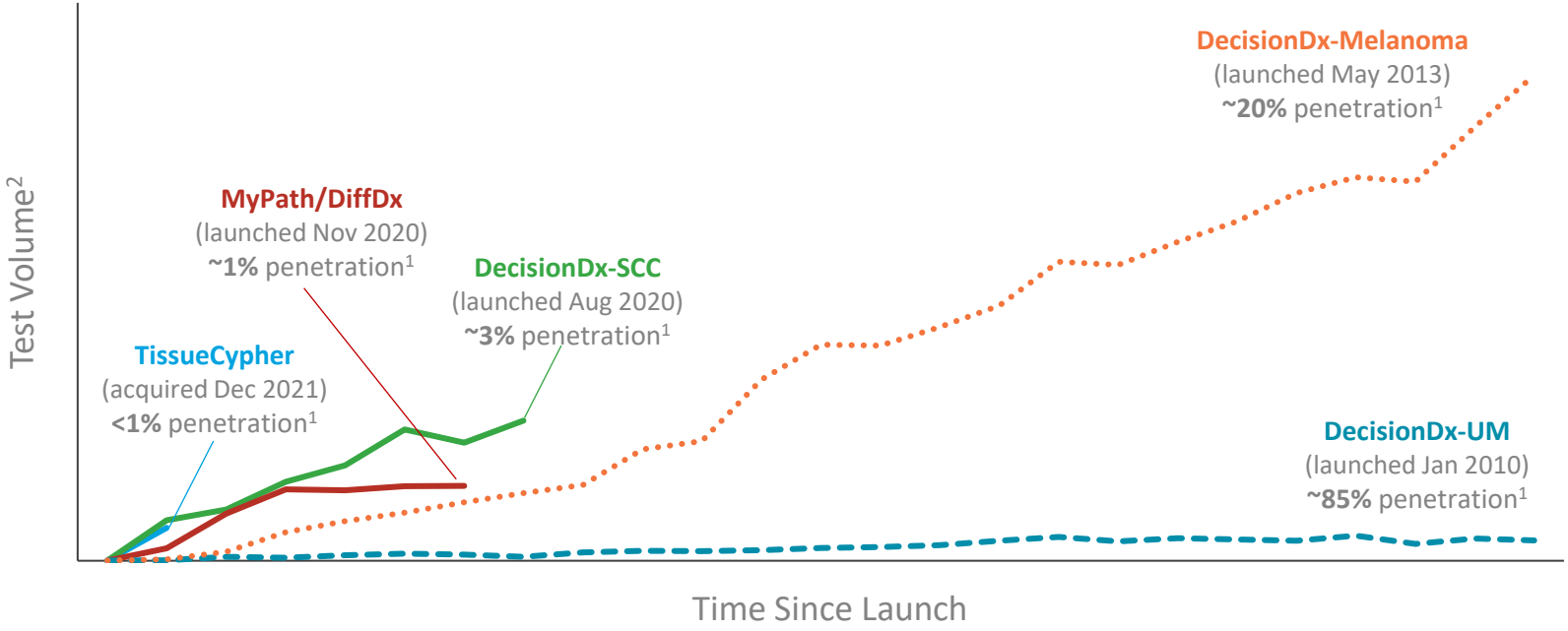
[1]Year-over-year revenue growth starting in 2023 through 2025 [2]Consists of R&D, SG&A, Amortization of Acquired Intangible Assets
[3]We expect to reach net operating cash flow positivity by 2025

Excellence of Execution: Legacy Uveal Melanoma Test is Standard-of-Care, Skin Cancer Tests Showing Strong Adoption

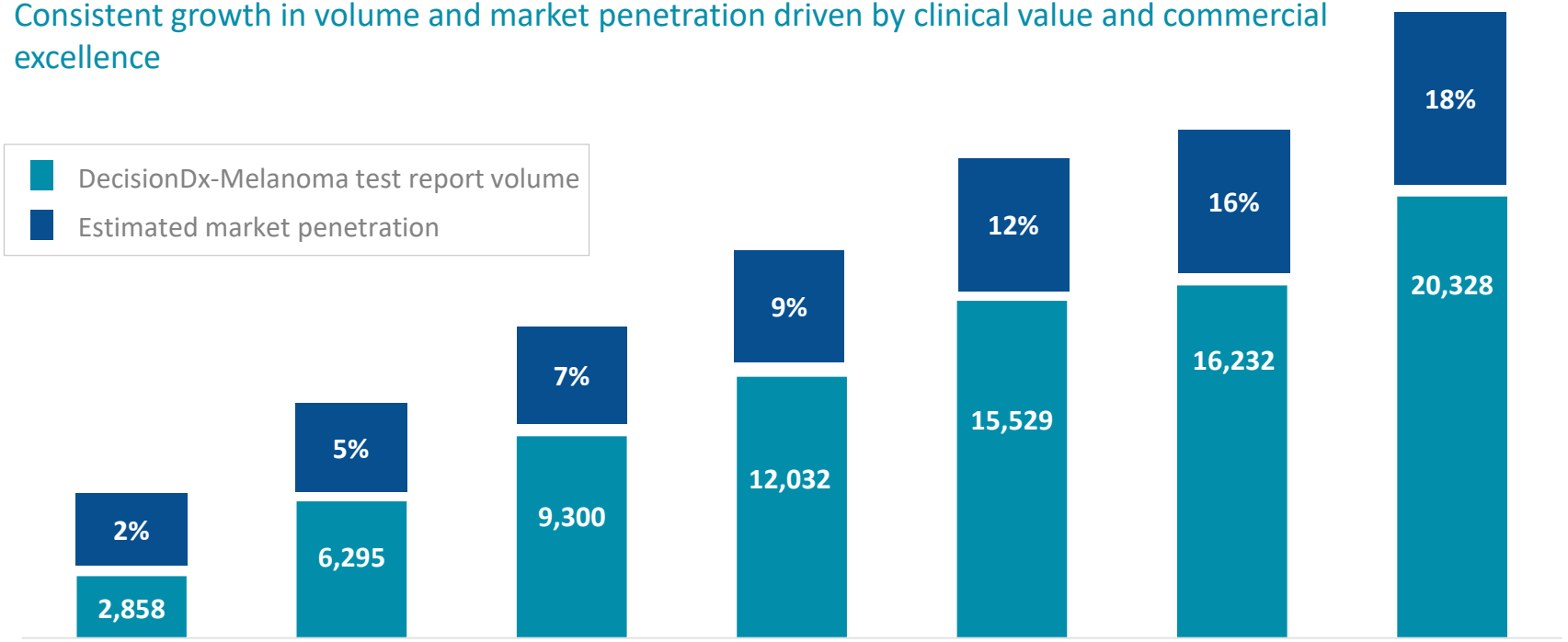


We expect each of our tests to reach at least 50%-60% penetration at maturity

[1]Penetration as of 6/30/22; data on file, Castle Biosciences
[2]Test volumes rebased to time of launch/acquisition

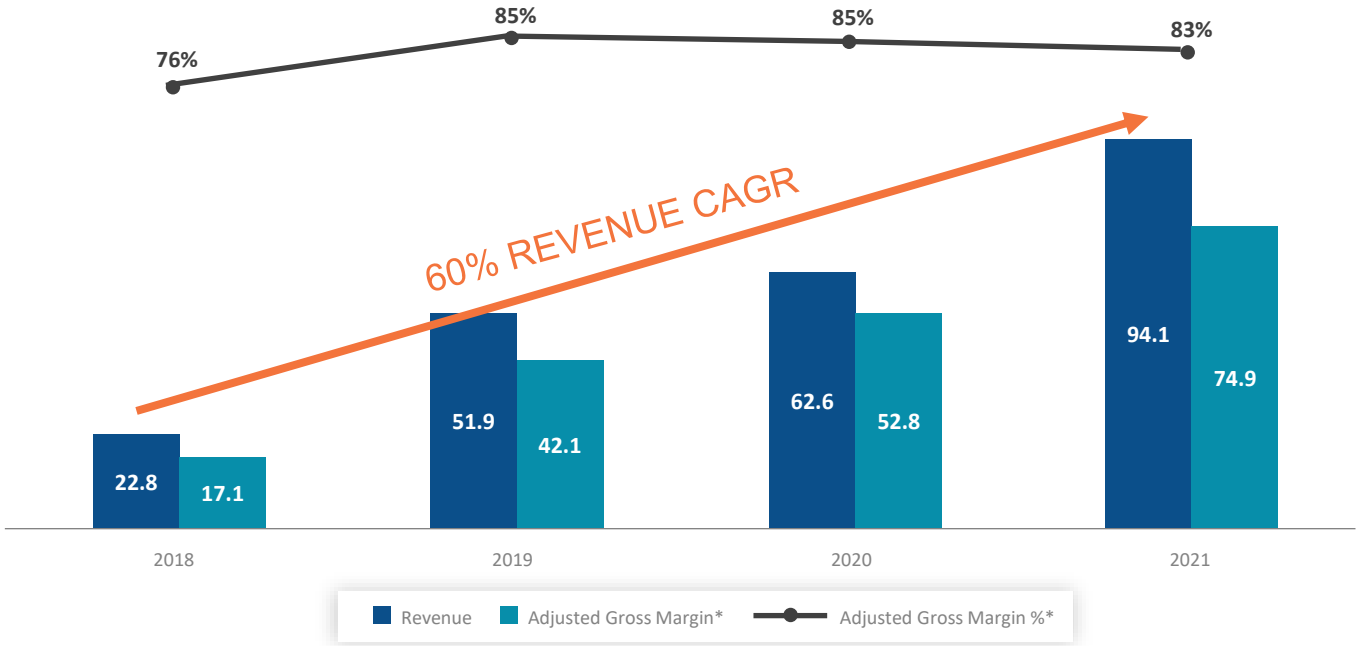
DecisionDx-Melanoma Adoption Since Launch

Consistent growth in volume and market penetration driven by clinical value and commercial excellence



Estimated penetration percentage calculated based on 130,000 melanoma diagnoses annually for 2015-2019; due to COVID-19, diagnoses were down 20% for 2020 and down 11% for 2021; [1]10 of the outside sales territories in 2020 were dedicated to our diagnostic GEP tests before being merged into the Dermatology-facing commercial team in 2021

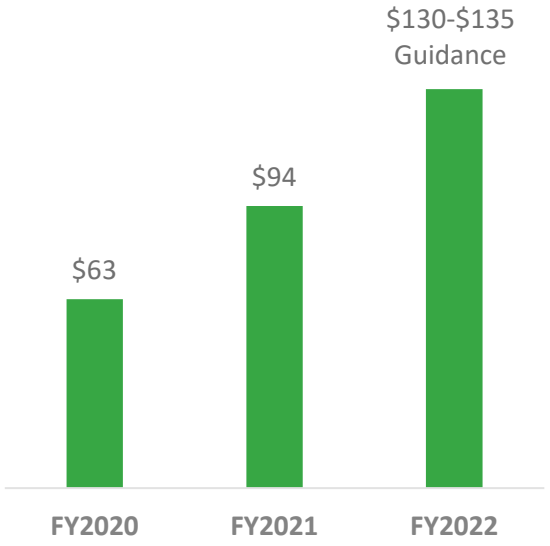
Strong Revenue CAGR of 60% Drives Exceptional Adjusted Gross Margins



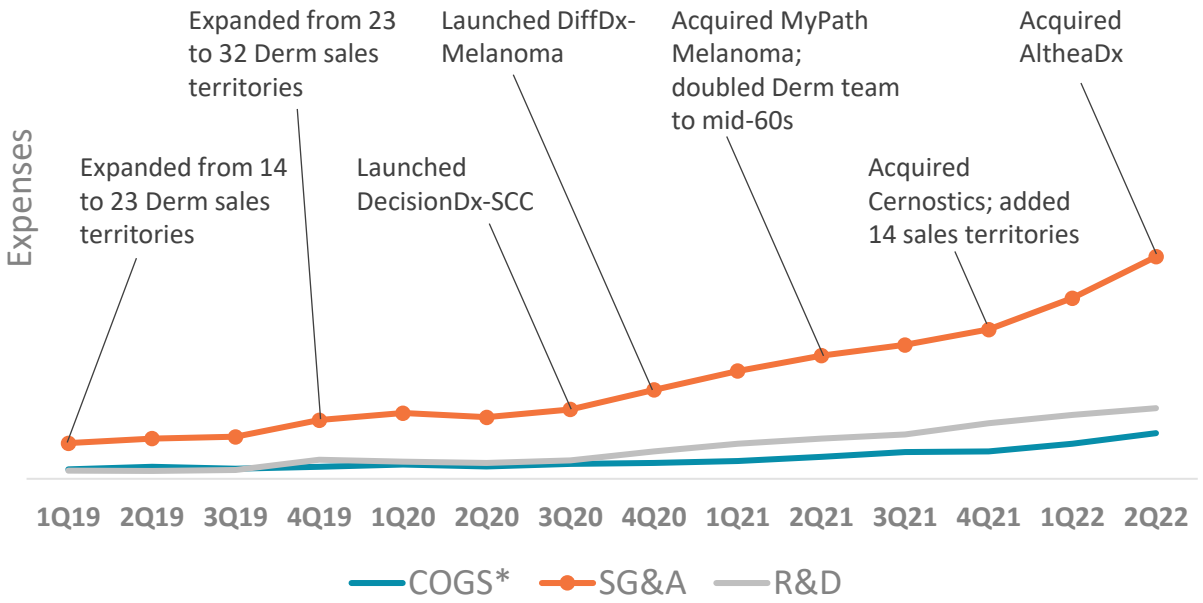
*See Non-GAAP reconciliations at the end of this presentation.

Product Launches, Focused Investments Expected to Drive Revenue Growth

Full-Year Revenue (millions)



Quarterly Operating Expenses



*Exclusive of amortization of acquired intangible assets

Strong Balance Sheet Keeps Us Positioned Well for Long-term Growth

Strong cash position and no debt

	June 30, 2022	December 31, 2021
Cash and cash equivalents	$273,166	$329,633
Accounts receivable, net	22,606	17,282
Other current assets	9,140	6,828
Total current assets	304,912	353,743
Long-term assets	153,468	108,829
Total assets	**$458,380**	**$462,572**
Accounts payable	3,281	2,546
Accrued compensation	14,850	15,483
Operating lease liabilities	1,211	1,179
Other accrued and current liabilities	8,177	5,678
Total current liabilities	27,519	24,886
Long-term liabilities	9,201	25,946
Total liabilites	36,720	50,832
Total stockholder's equity	421,660	411,740
Total liabilities and stockholder's equity	**$458,380**	**$462,572**

(numbers in thousands)

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Disciplined Approach to Capital Allocation

- Focused R&D efforts to build evidentiary support and develop pipeline tests
- Commercial optimization
- To a lesser priority, tuck-in acquisitions **in the areas** of our current three franchises

Expected net operating cash flow positivity by 2025

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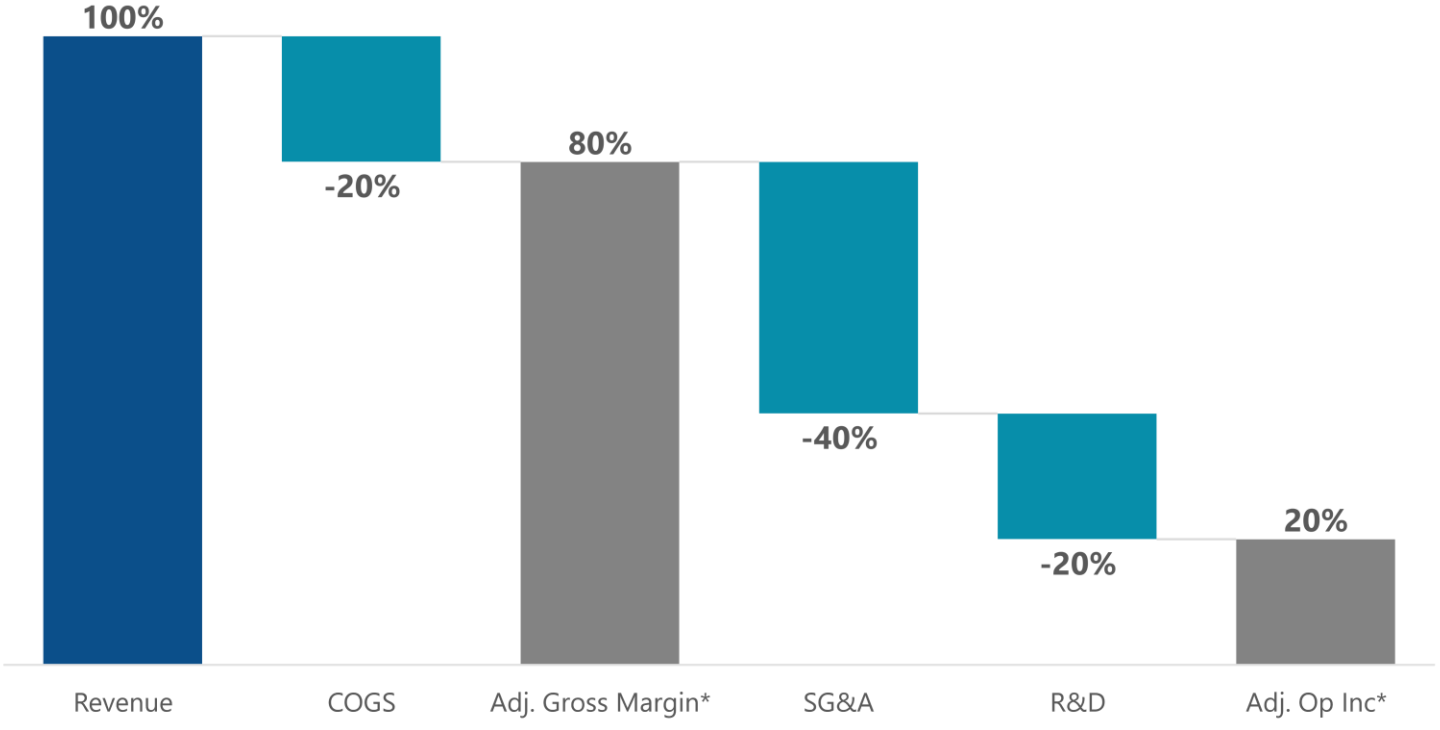
Castle's Expected Common-Size P&L Model at Maturity Demonstrates Efficient Execution



*See Non-GAAP reconciliations at the end of this presentation.

Key Financial Highlights Takeaways

The demonstrated value and utility of our tests, along with our ongoing commercialization efforts, have driven greater adoption and robust test volume growth

Our growing revenue base puts us in a position to continue to build on our strong gross margin performance

Our focused growth investments, including acquisitions, have necessarily driven higher operating expenses, but we expect these near-term expenses to contribute to long-term profitability

Our long-term growth is further supported by our debt-free balance sheet and emphasis on measured capital spending

By 2025, we expect:

Total revenue of between $255 million to $330 million

Adjusted Gross Margins in the range of 80% to 85%

Combined R&D, SG&A and amortization of acquired intangible assets to comprise roughly 75% to 85% of revenue

Net operating cash flow to be positive

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Summary

Derek Maetzold

Upcoming Milestones

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

Expected finalization of Palmetto/Meridian LCD for DiffDx-Melanoma by end of Q2 2023; MyPath Melanoma is already covered by full reimbursement by Medicare

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

Expected closure of San Diego lab by end of 2022, folding operations into our Phoenix location

Expected Palmetto/MolDx draft LCD for DecisionDx-SCC

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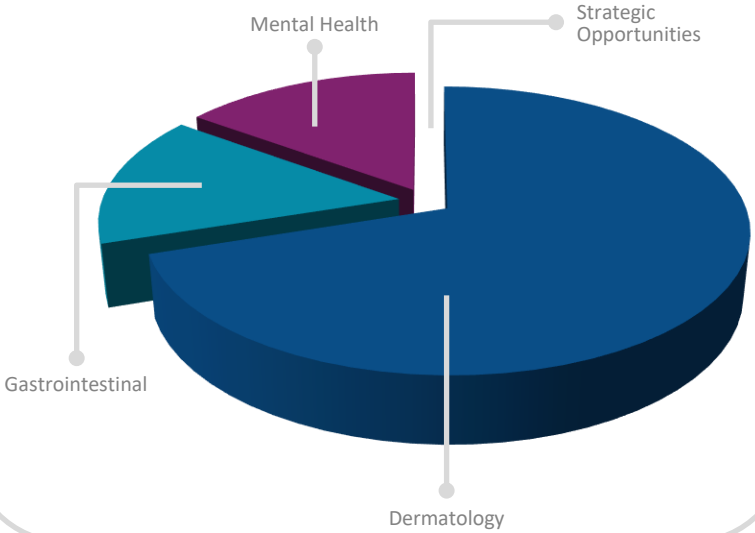
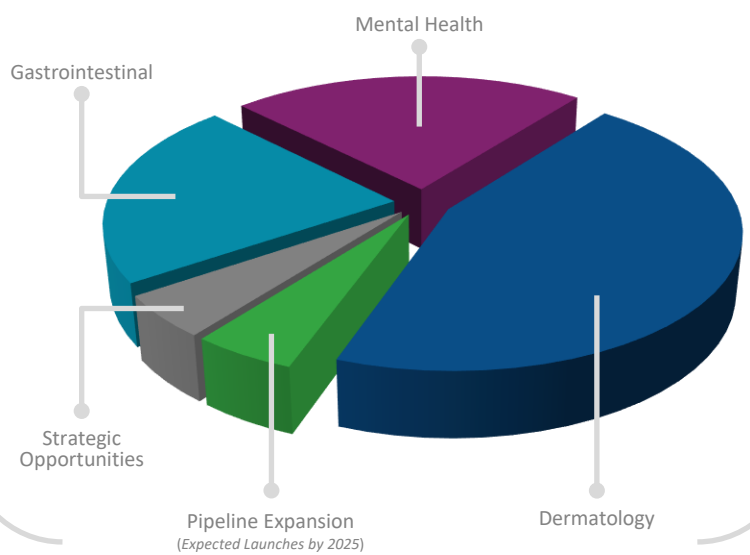
Driving Long-Term Growth through Strong Execution and our Operational Guideposts

Exceptional Employees, Continuous Evolution & Improvement and Customer & Solution Centric

Near- to Mid-term Growth



Mid- to Long-term Growth



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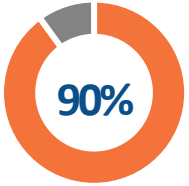
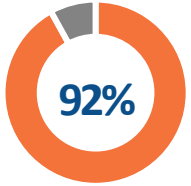
Castle's Innovative Tests Provide Value for Patients

Data from two patient studies conducted in collaboration with the Melanoma Research Foundation

DecisionDx ▸Melanoma

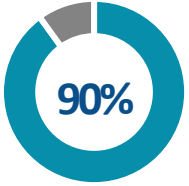


Wanted prognostic information about their melanoma tumors at diagnosis[1]

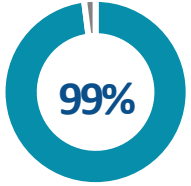


Felt the testing was useful[1]

DecisionDx ▸UM



Wanted prognostic information at diagnosis[2]



Indicated they gained value from their test result[2]

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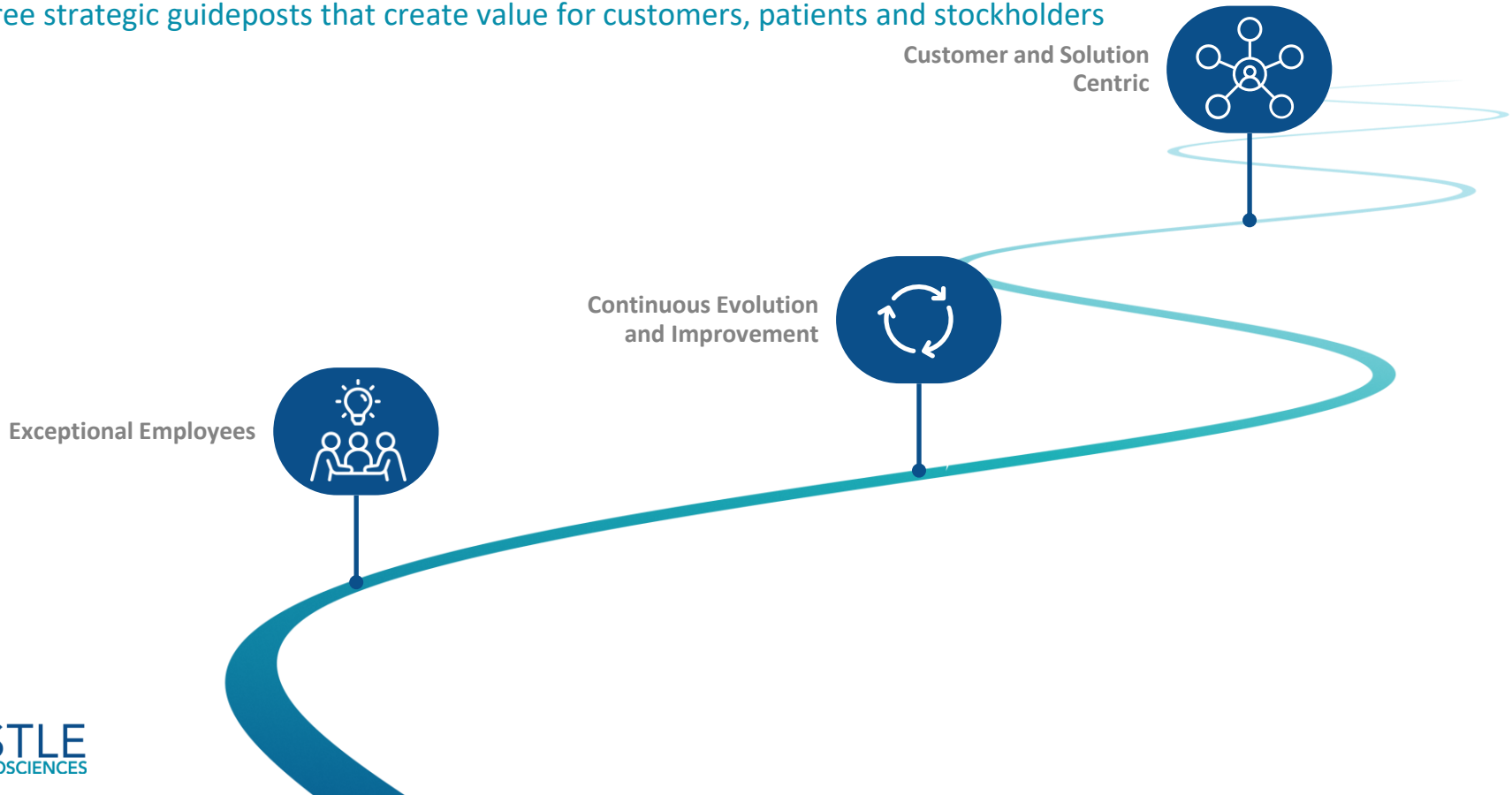
[1]Ahmed et al. *Cancer Medicine* 2022; some values have been rounded [2]Williams et al. *Melanoma Management* 2022 (ahead of publication)

Castle Is Focused on Improving Health through Innovative Tests That Guide Patient Care

Three strategic guideposts that create value for customers, patients and stockholders



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Q&A

Derek Maetzold
Founder, President & Chief Executive Officer

Frank Stokes
Chief Financial Officer

Matthew Goldberg, M.D.
Medical Director

Craig Munroe, M.D.
GI Medical Director

Camilla Zuckero
Vice President, Investor Relations & Corporate Affairs

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Investor Day

Thank you for joining

September 20, 2022

Use Of Non-GAAP Financial Measures (Unaudited)

In this presentation, we use the metrics of Adjusted Revenue, Adjusted Gross Margin and Adjusted Operating Cash Flow, which are non-GAAP financial measures and are not calculated in accordance with generally accepted accounting principles in the United States (GAAP). Adjusted Revenue 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 Operating Cash Flow excludes the effects of repayments to Medicare of COVID-19 government relief advancements to healthcare providers.

We use Adjusted Revenue, Adjusted Gross Margin and Adjusted Operating Cash Flow 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 Adjusted Revenue and Adjusted Gross Margin are also useful to investors because they provide additional information on current-period performance by removing the effects of revenue adjustments related to tests delivered in previous periods and, with respect to Adjusted Gross Margin, acquisition-related intangible asset amortization, which we believe may facilitate revenue and gross margin comparisons to historical periods. 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 payments, which we believe are not indicative of our ongoing operations. 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 cash (used in) provided by operating activities reported in accordance with GAAP and should be considered in conjunction with our financial information presented on a GAAP basis and language from our earnings press release. 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 slides that follow. We are not providing a target for or a reconciliation of Adjusted Gross Margin.

Reconciliation of Non-GAAP Financial Measures (Unaudited)

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

(in thousands)	3 Months Ended - June 30, 2022	3 Months Ended - June 30, 2021	6 Months Ended - June 30, 2022	6 Months Ended - June 30, 2021
Adjusted revenue				
Net revenues (GAAP)	$34,838	$22,758	$61,690	$45,571
Revenue associated with test reports delivered in prior periods	(578)	166	300	(5,092)
Adjusted revenue (Non-GAAP)	$34,260	$22,924	$61,990	$40,479
Adjusted gross margin				
Gross margin (GAAP)[1]	$25,055	$18,805	$44,315	$38,590
Amortization of acquired intangible assets	2,097	256	3,745	256
Revenue associated with test reports delivered in prior periods	(578)	166	300	(5,092)
Adjusted gross margin (Non-GAAP)	$26,574	$19,227	$48,360	$33,754
Gross margin percentage (GAAP)[2]	71.9%	82.6%	71.8%	84.7%
Adjusted gross margin percentage (Non-GAAP)[3]	77.6%	83.9%	78.0%	83.4%

[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 adjusted gross margin (Non-GAAP) divided by adjusted revenue (Non-GAAP)

CASTLE BIOSCIENCES

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 104 for further information regarding the Company's use of non-GAAP financial measures.

(in thousands)	3 Months Ended - June 30, 2022	3 Months Ended - June 30, 2021	6 Months Ended - June 30, 2022	6 Months Ended - June 30, 2021
Adjusted operating cash flow				
Net cash used in operating activities (GAAP)	$(9,001)	$(6,438)	$(30,431)	$(10,069)
Medicare advance payment[1]	—	2,173	—	2,173
HHS provider relief funds[2]	—	—	—	(1,882)
Adjusted operating cash flow (Non-GAAP)	$(9,001)	$(4,265)	$(30,431)	$(9,778)

[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 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).

CASTLE BIOSCIENCES

Reconciliation of Non-GAAP Financial Measures (Unaudited)

The table below presents the reconciliation of adjusted revenue and adjusted gross margin, which are non-GAAP financial measures. See slide 104 for further information regarding the Company's use of non-GAAP financial measures.

(in thousands)	2018	2019	2020	2021
Adjusted revenue				
Net revenues (GAAP)	$22,786	$51,865	$62,649	$94,085
Revenue associated with test reports delivered in prior periods	(343)	(2,493)	(176)	(3,324)
Adjusted revenue (Non-GAAP)	$22,443	$49,372	$62,473	$90,761
Adjusted gross margin				
Gross margin (GAAP)[1]	$17,489	$44,555	$52,964	$76,305
Amortization of acquired intangible assets	—	—	—	1,958
Revenue associated with test reports delivered in prior periods	(343)	(2,493)	(176)	(3,324)
Adjusted gross margin (Non-GAAP)	$17,146	$42,062	$52,788	$74,939
Gross margin percentage (GAAP)[2]	76.8%	85.9%	84.5%	81.1%
Adjusted gross margin percentage (Non-GAAP)[3]	76.4%	85.2%	84.5%	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 adjusted gross margin (Non-GAAP) divided by adjusted revenue (Non-GAAP)

CASTLE BIOSCIENCES

Reconciliation of Non-GAAP Financial Measures (Unaudited)

The table below presents the reconciliation of adjusted operating income, which is a non-GAAP financial measure. See slide 104 for further information regarding the Company's use of non-GAAP financial measures.

Adjusted gross margin	
Gross margin (GAAP)[1]	76%
Amortization of acquired intangible assets	4%
Adjusted gross margin (Non-GAAP)	80%
Adjusted operating income	
Operating income (GAAP)[2]	16%
Amortization of acquired intangible assets	4%
Adjusted operating income (Non-GAAP)	20%

[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 as a percentage of net revenues.

[2]Calculated as net revenues (GAAP) less the sum of cost of sales (exclusive of amortization of acquired intangible assets), marketing and administrative expense, research and development expense, and amortization of acquired intangible assets as a percentage of net revenues.

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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