CASTLE BIOSCIENCES

Transforming Disease Management

February 28, 2022

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 the effects of the COVID-19 pandemic on our business and our efforts to address its impact on our business; any estimated sizes of the total addressable markets of our current or future commercial and pipeline products within our dermatologic and GI franchises; our revenue outlook for the 2022 fiscal year, including any additional financial or operational metrics or related expectations with respect to future performance; 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 launch dates for tests in our pipeline expansion and estimates regarding their total addressable markets or future success; expectations regarding LCD effective dates and reimbursement capabilities; our ability to utilize existing relationships and build a suite of complementary tests in a single call point; 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; our sales team's ability to achieve optimal productivity; 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," "estimates," "expects," "intends," "may," "plans," "projects," "will," "would" 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 results and findings may contradict earlier study results and findings, including with respect to the diagnostic and prognostic tests discussed in this press release, 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 in our Annual Report on Form 10-K for the twelve months ended December 31, 2021, 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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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:

Trust, Excellence, Collaboration, Integrity, Innovation and Excitement

Improving Health Through Innovative Tests That Guide Patient Care

Castle Team

345 Total employees

106 Sales & marketing team members

76 Laboratory testing operations team members

65 Research & development team members

A Diagnostic Leader

Strong financial position, driven by investments in our growth pillars and commercial excellence

Diversified portfolio of tests that answer clinical questions and provide actionable information

Data driven with a robust R&D and clinical research engine that address areas of unmet clinical need

Culture of teamwork and innovation, built on a **patient-centric mindset**

Robust Data Supporting our Tests

Peer-reviewed publications

35+ DecisionDx MELANOMA

9 DecisionDx-SCC

12 myPath Melanoma DecisionDx DiffDx-Melanoma

21 DecisionDx-UM

8 tissuecypher BARRETT'S ESOPHAGUS ASSAY

Data as of 12/31/21; total employee count also includes 98 general & administrative team members

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Financial Performance Summary 2021

	2021	2020
Revenue	**$94.1M**	$62.6M
Adj. Revenue[1]	**$90.8M**	$62.5M
Total GEP test reports[2]	**28,118**	18,185
Total Derm test reports[2]	**26,500**	16,790
Operating Cash Flow	**$(19.0)M**	$9.9M
Adj. Operating Cash Flow[1]	**$(12.5)M**	$1.5M
Gross Margin	**81.1%**	84.5%
Adj. Gross Margin[1]	**82.6%**	84.5%
Cash & Cash Equivalents	**$330M** as of 12/31/2021	$410M as of 12/31/2020

[1]See Non-GAAP reconciliations at the end of this presentation.
[2]DecisionDx-SCC was launched on 8/31/20; DecisionDx DiffDx-Melanoma was launched on 11/2/20

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Castle Remains Focused On Transforming Disease Management

Strategic principles that create value for customers, patients and stockholders

Address areas with unmet clinical need

Leverage advanced technologies for innovative tests

Provide robust data to support the clinical value of our tests

Accelerate test adoption through commercial excellence

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Driving Long-Term Growth Through A Strong Derm Foundation, Pipeline and Strategic Opportunities

Near-to Mid-term Growth

2022-2023

- DecisionDx MELANOMA
- DecisionDx-SCC
  (Potential LCD effective in 2023)
- myPath Melanoma
- DecisionDx DiffDx-Melanoma
  (Potential LCD effective in 2023)
- tissuecypher BARRETT'S ESOPHAGUS ASSAY
- **Strategic Opportunities**

Mid-to Long-term Growth

2024 and beyond

- DecisionDx MELANOMA
- DecisionDx-SCC
- DecisionDx myPath Melanoma DiffDx-Melanoma
- tissuecypher BARRETT'S ESOPHAGUS ASSAY
- **Pipeline Expansion**
  (Expected launches ~2025)
- **Strategic Opportunities**

Strategic Opps

Gastrointestinal

Dermatology

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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

DecisionDx MELANOMA

DecisionDx-SCC

myPath Melanoma

DecisionDx-UM

DecisionDx DiffDx-Melanoma

tissuecypher BARRETT'S ESOPHAGUS ASSAY

Inflammatory Pipeline Test

Patient Care Journey	Screening	Diagnostic Support	Risk Stratification	Therapy Response	MRD/Recurrence Monitoring

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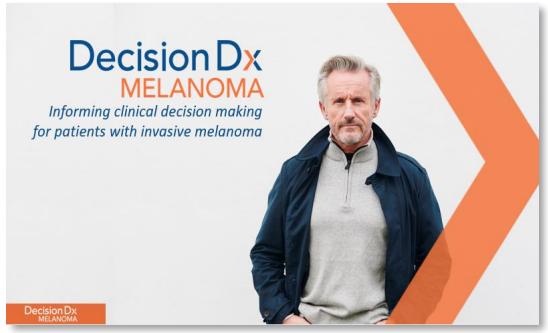
Pillars Of Our Growth Plan

Consistent execution furthers our leading position in dermatology and in the Dx space

Strong Core Derm Business



- Continuing provider education
- Optimizing commercial team
- Evolving our go-to-market strategy (EMA, VA)
- NCI/SEER collaboration

+

Pipeline Initiatives

- Ability to answer clinical questions/impact patient care
- Utilizing our areas of expertise (genomics, spatialomics, AI) to develop innovative tests
- Focusing on complementary/ adjacent disease states

+

Strategic Opportunities

myPath Melanoma

cernostics
PROVIDING DEEPER TISSUE INSIGHTS

- Areas where we can utilize our commercial success
- Potential to create a suite of tests in a single call point
- Ability to answer clinical questions/impact patient care
- Early reimbursement wins

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2021 Key Accomplishments

- Achieved strong, consistent year-over-year growth, both in our revenue (+50%) and test report volume (+55%), with net cash used in operating activities of $19 million and adjusted operating cash flow use of $13 million
- Doubled our dermatology-facing commercial team and added to our commercial dermatology offerings with the acquisition of myPath Melanoma
- Expanded evidence supporting our portfolio of tests to drive clinical usage with 15 peer-reviewed publications and initiated our collaboration with NCI/SEER
- Began development of our GI franchise through the acquisition of Cernostics and their TissueCypher test for use in Barrett's esophagus
- Published our inaugural ESG report, helping us progress our ESG initiatives and demonstrating our commitment to patients, employees, stockholders and our communities

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

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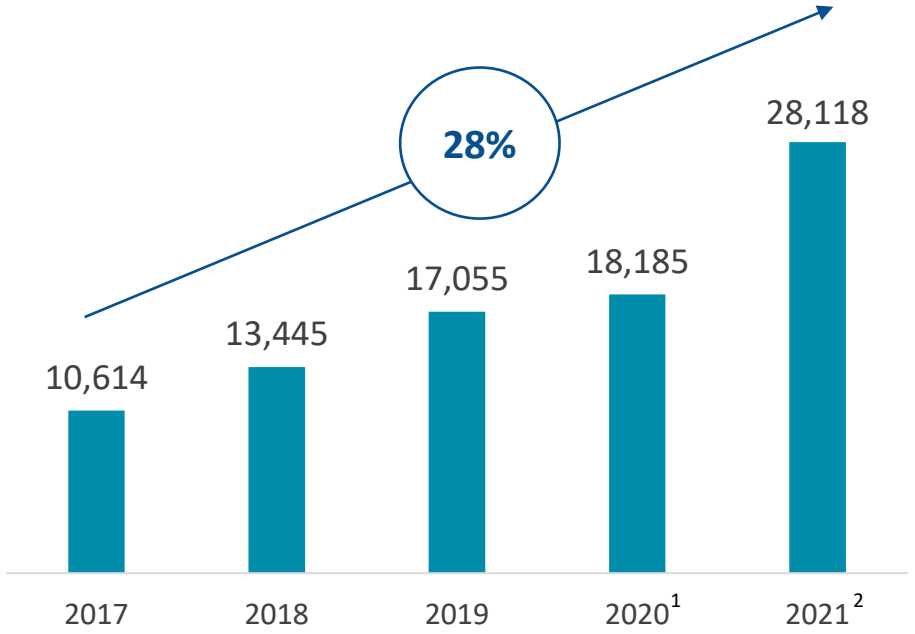
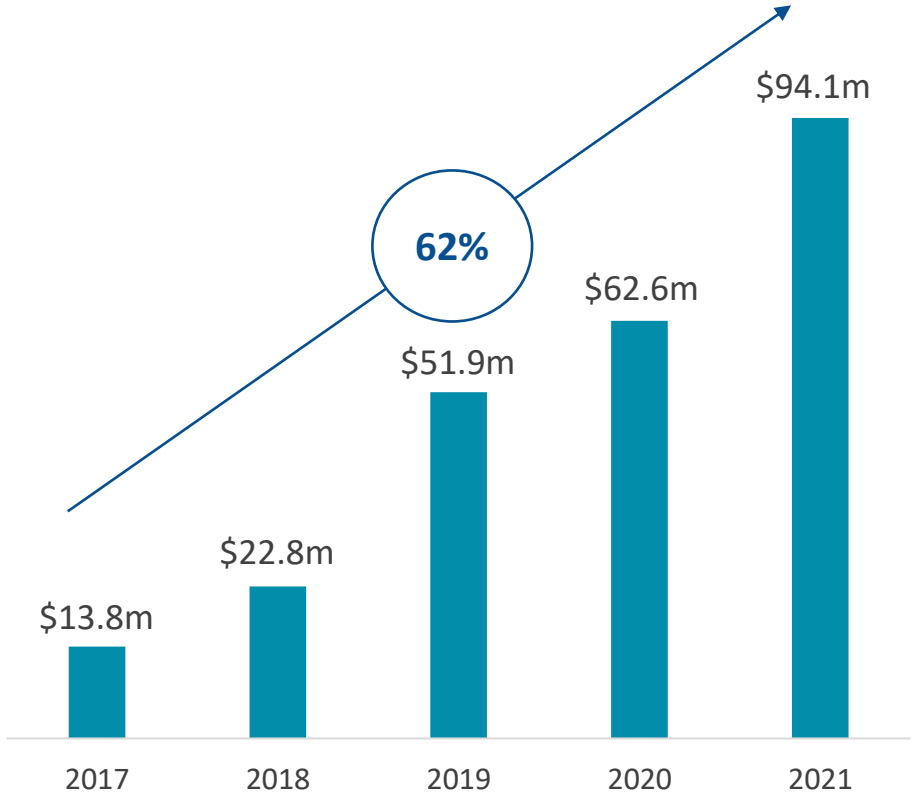
Consistent Execution On Growth Initiatives Supports Long-Term Growth

2017-2021 Total Test Report Volume CAGR



2017-2021 Revenue CAGR



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

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Full-Year 2022 Guidance

	February 28, 2022	Key Drivers
Revenue	$115 - $120 million	
Cost of Sales (exclusive of amortization of acquired intangible assets)	65%-75% growth	Scaling of Pittsburgh lab; preparation for volume ramp for TissueCypher, DecisionDx-SCC and DiffDx-Melanoma ahead of reimbursement
R&D Expense	50%-60% growth	Continued acceleration in R&D to support our derm, GI and pipeline tests, including increase in clinical research and additional headcount
SG&A Expense	30%-35% growth	Addition of gastroenterology team and continued build in dermatology
Stock Based Comp	$35-40 million	Primarily due to increase in headcount to support growth, with pace of additional employees increasing in recent years and 2022

Percentage increases compared to the year ended 12/31/21; Cost of sales, R&D and SG&A expense growth includes stock-based comp.

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Estimated ~$6.6B U.S. Total Addressable Market[1]

In market and pipeline tests, across dermatologic and gastrointestinal franchises

Dermatologic Franchise

Cutaneous melanoma/ risk of metastasis

~130k
Patients classified as Stage I, II or III[2]

~$540M

DecisionDx MELANOMA

Cutaneous squamous cell carcinoma/ risk of metastasis

~200k
Patients w/ high-risk features[2]

~$820M

DecisionDx-SCC

Suspicious pigmented lesions/melanoma status

~300k
Patients w/ indeterminant biopsy[2]

~$600M

myPath Melanoma DecisionDx DiffDx-Melanoma

Pipeline Test - Inflammatory

~450k
Patients eligible for systemic therapies

~$1.9B

Additional Derm Pipeline Tests

To be announced

~$1.7B

GI Franchise

Barrett's esophagus/ risk of progression to esophageal cancer

384K
Patients receiving upper GI endoscopies/year who meet the intended use criteria for TissueCypher[3]

~$1B

tissuecypher BARRETT'S ESOPHAGUS ASSAY

[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]384,000 upper GI endoscopies/year with confirmed dx of BE (ND, IND, LGD) x $2,513 = U.S. only TAM of ~$1 billion

2022 Anticipated Catalysts

- Potential DecisionDx-SCC and DecisionDx DiffDx-Melanoma draft LCD
- Potential expansion of commercial teams to further accelerate test adoption and volume growth in GI and Derm
- Continued evidence development, data presentations and peer-reviewed publications to support the value of our test and increase adoption with providers and commercial payers
- Pipeline updates in Derm franchise

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GI/Cernostics Integration Update

Fueling mid- and long-term growth with TissueCypher® platform and GI franchise

- New GI commercial team of ~ 14 outside territories hired, trained and in the field in January 2022, GI focused medical science liaisons and internal sales associates hired
- Year-to-date 2022, two abstracts for GI conferences (podium presentations at ESGE Days 2022 and DDW 2022) and one peer-reviewed publication accepted
- Lab floorplan and workflow reconfigurations have increased efficiencies with more progress expected throughout 2022
- Leveraging spatialomics expertise to identify pipeline opportunities in GI and dermatology
- Planned capex investments (lab expansion and additional headcount) expected to allow for further enhancements to automation, a significant increase to throughput and provide support for potential future GI tests off the TissueCypher spatialomics platform

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

16
Ongoing clinical research studies

341
Committed/ contributing clinical research sites at year-end 2021

7,800+
Patients enrolled in studies at year-end 2021

~12,000
Patients enrolled in studies over lifetime of Castle

20,000+
Additional patient's data we anticipate analyzing in CM studies in 2022

CM = cutaneous melanoma

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Accelerating Investments In Clinical Development

Generating data that supports the clinical value of our tests and supports provider and payer adoption

DecisionDx MELANOMA	DecisionDx-SCC	DecisionDx myPath Melanoma DiffDx-Melanoma	tissuecypher BARRETT'S ESOPHAGUS ASSAY
4 *Ongoing studies*	**3** *Ongoing studies*	**3** *Ongoing studies*	**3** *Ongoing studies*
102 *Committed sites*	**144** *Committed sites*	**25** *Committed sites*	**11** *Committed sites*
~1,400 *Patients enrolled*	**~3,100** *Patients enrolled*	**~3,250** *Patients enrolled*	**~630** *Subjects[1] enrolled*

Upcoming Q1-Q2 Data Presentations

• SSO 2022 • AAD 2022	• AAD 2022 • ACMS 2022		• ESGE Days 2022 • DDW 2022

[1]Subjects includes patients and physicians

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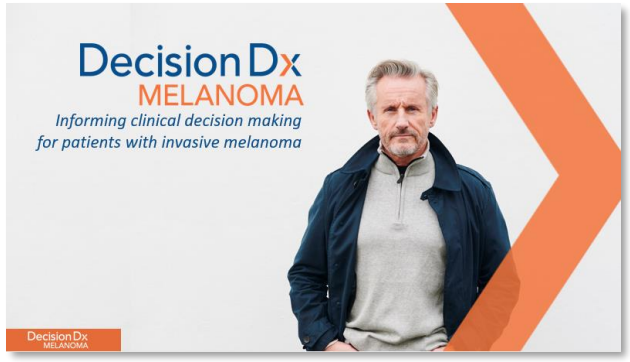
First To Market Dermatologic Franchise, Additional Growth Opportunities

Diagnostic Support

Risk-Stratification



Therapy Response[1]

[1]*Target launch anticipated by the end of 2025*

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DecisionDx-Melanoma: Precision Risk Stratification Based on Tumor Biology Informs Treatment Plans

DecisionDx MELANOMA

Market Snapshot	Clinical Questions *(post-melanoma diagnosis)*	Clinical Utility	Transforming Disease Management
~$540M revenue opportunity[1] **~130k patients** classified as Stage I, II or III[2]	Is the risk of SLN-positivity high enough to warrant referral for the SLNB surgery?	Accurately identifies those at ***low and high risk for a positive SLN***[3]	DecisionDx-Melanoma ***could result in 74% fewer SLNB surgeries***[7], potentially saving the U.S. healthcare system $250M[4,5] ***Why? More precise risk prediction*** – DecisionDx-Melanoma identified 27.7% of patients as low risk (<5%) of SLN positivity, compared to only 8.5% using T-Stage[3]
	What is the individual risk of recurrence?	Provides ***personalized risk of recurrence*** to give guidance for patient follow-up and treatment intensity decisions	4 consecutive clinical impact studies show a ***47-53% change in management decisions*** (i.e., imaging and labs, SLNB guidance, clinical visit frequency, referrals) based on DecisionDx-Melanoma results[6]

SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy. Source: NCCN Guidelines for Cutaneous Melanoma v3.2020 [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.
[3]Whitman et al. *JCO Precision Oncology* 2021 [4]Vetto et al. Future Oncol 2019. [5]Clearview health economic model, data on file
[6]Four consecutive clinical impact studies showed 47-53% change in risk-of-recurrence-based management based on results of testing with DecisionDx-Melanoma: Berger, et al. 2016 Curr Med Res Opin; Dillon et al. 2018 Skin; Farberg et al. 2017 Jrnl Drugs Derm; Schuitevoerder, et al. 2018 Jrnl Drugs Derm.
[7] For patients with melanomas of less than or equal to 2.0 mm thick

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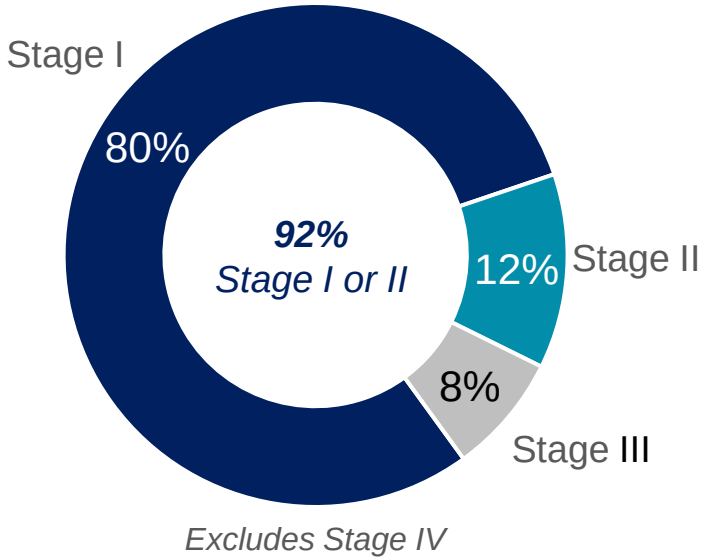
Current Melanoma Staging Misses Patients With Aggressive Tumor Biology

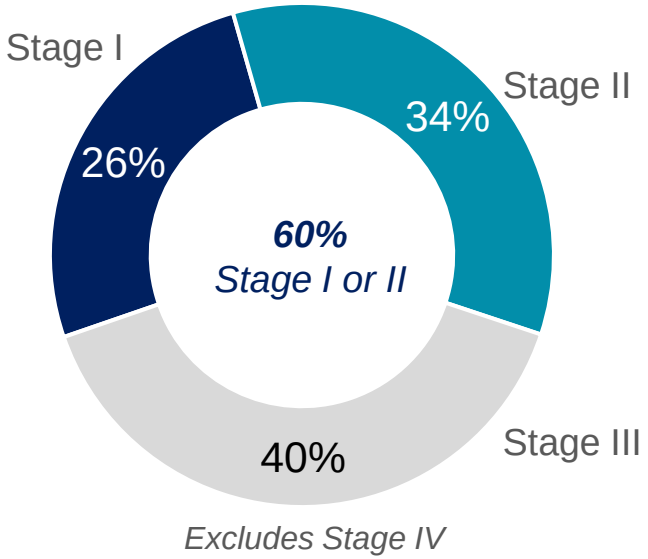
DecisionDx MELANOMA

Stage at Diagnosis



Excludes Stage IV

Melanoma **Deaths** by Stage at Diagnosis



Excludes Stage IV

The majority of melanoma deaths occur in patients who were diagnosed at Stage I or II

[1]AJCC v7 *J Clin Oncol* 2009; [2]SEER data release 2017; [3]Morton et al. *N Engl J Med* 2014; [4]Whiteman et al. *J Invest Dermatol* 2015; [5]Shaikh et al. *J Natl Cancer Inst* 2016; [6]Poklepovic and Carvajal. *ONCOLOGY* 2018; [7]Ibrahim et al. *Ann Surg Oncol* 2020

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DecisionDx-Melanoma Is Supported By Significant Scientific Evidence

DecisionDx MELANOMA

6,000+
Patients included in studies including ***independent validation***

35+
Peer-reviewed, published studies including ***2 meta-analyses***

90,000+
Patients with a ***DecisionDx-Melanoma*** order from more than ***9,300 clinicians***

1A
Level 1A evidence*

50%
Demonstrated change in management for 1 of 2 patients tested

Medicare+
Covered by Medicare and multiple private insurers with an ***industry-leading*** patient assistance program

*According to sort system, used by American Academy of Dermatology
Following a diagnosis of cutaneous melanoma, providers make two important treatment decisions – whether to recommend SLNB and what type/frequency of follow up should be used.

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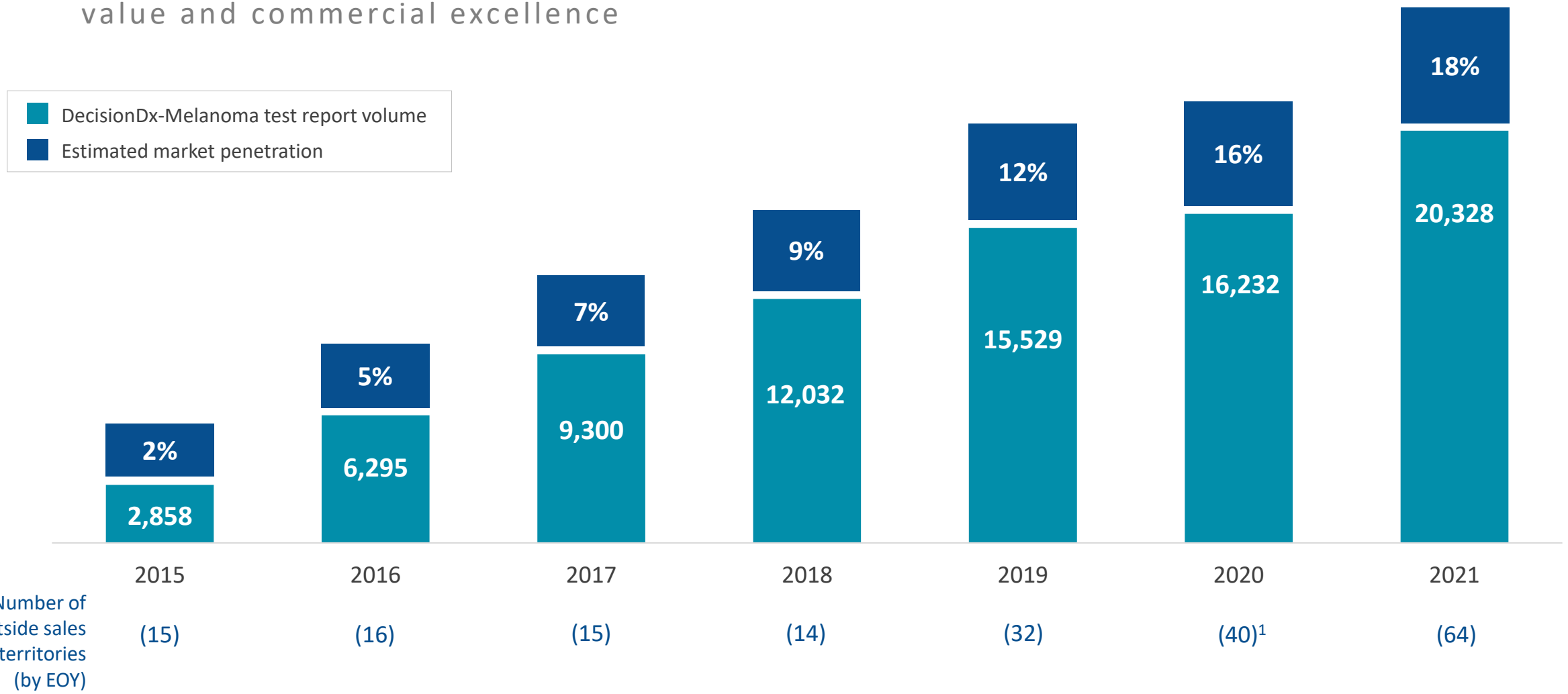
DecisionDx-Melanoma Adoption Since Launch

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



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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 Comprehensive Diagnostic Offering before being merged into the Dermatology-facing commercial team in 2021

NCI/SEER Data Linked with DecisionDx-Melanoma Test Results

Data analysis of the first cohort of patients 65 years or older[1]

DecisionDx MELANOMA

Data further strengthens independent, risk-stratification value of testing with DecisionDx-Melanoma

10x increase in death rate for patients with a high-risk result

(12.3% death rate for a Class 2B (high-risk) result compared to 1.5% for a Class 1A (low risk) result)

Data provides real world evidence that patients tested with DecisionDx-Melanoma had improved overall survival rates vs. untested patients

0.66 hazard ratio | **0.002** p-value

(a hazard ratio less than 1.0 demonstrates improved survival in patients tested with DecisionDx-Melanoma)

[1]Initial data analysis following data linkage included an unselected, prospectively tested population of Medicare-eligible patients 65 years and older, consistent with prior study cohorts
‡Hazard ratio (HR) was computed using the untested patients as reference for 31-GEP testing. An HR less than 1.0 demonstrates improved survival in 31-GEP tested patients. Diagnosis date 2016 and onward. †MSLT-116: Multicenter Selective Lymphadenectomy Trial-1. SLNB: sentinel lymph node biopsy. WLE: wide local excision. SE: standard error. †Intermediate thickness tumors (1.2-3.5 mm).
[1]Bailey C. et al. "31-gene expression profile testing survival benefit in a population-based analysis of cutaneous melanoma patients ≥65 years of age"Poster at 2022 Winter Clinical Dermatology Conference

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DecisionDx-SCC: Predicts Metastatic Risk for SCC Patients With One Or More Risk Factors

Market Snapshot	Clinical Question *(post-SCC diagnosis)*	Clinical Utility	Transforming Disease Management
~$820M revenue opportunity[1] **~200k patients** with high-risk features[2]	Who is really at low risk or high risk for metastasis?	***Predicts metastatic risk*** for individual SCC patients with one or more risk factors	***Improved accuracy of metastasis risk predictions compared to BWH and AJCC8 staging*** Significantly greater specificity (Class 2B=96.9%) and sensitivity (Class 2-77.8%) compared to metrics for high-stage BWH and AJCC8
		Incorporation of DecisionDx-SCC can ***improve management decisions within established guidelines***	***Enhances revised NCCN risk stratification*** Class 2A results showed hazard ratios of >1.25x NCCN very high risk while class 2B results showed hazard ratios of >4.5x NCCN very high risk
		Proven ***significant and independent prognostic value*** for stratifying risk of metastasis in high-risk SCC patients	***DecisionDx-SCC Class 2B results have a higher positive predictive value*** (60%) ***than BWH*** (35.1%) ***and AJCC8*** (32.8%) Current SCC staging fails to identify >35% of cases that will go on to metastasize and over-stages >75% that will not

SCC = squamous cell carcinoma; NCCN = National Comprehensive Cancer Network (NCCN); BWH = Brigham and Women's Hospital; AJCC8 = American Joint Committee on Cancer Eighth Edition

[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 squamous cell carcinoma estimated at 1,000,000 with addressable market limited to carcinomas with one or more high risk features.

Wysong et al. JAAD 2020; Ibrahim et al. Future Oncology 2021; Data on file, Castle Biosciences

NCCN Guidelines for Squamous Cell Skin Cancer v1 2022, Likhacheva et al. Pract Radiat Oncol 2020, Farberg et al. CMRO 2020, Litchman et al. CMRO 2020, Teplitz et al. JDD 2019, Alam et al. JAAD 2018

DecisionDx-SCC Addresses the Unmet Need In High-Risk SCC Patients

Who is really at low risk or high risk for metastasis?

Deaths from SCC are now estimated to ***exceed those from melanoma***

~20% of SCC patients (200,000 annually) have ***one or more clinical*** or ***pathological risk factors***, and a subset will ***develop metastasis***

They suffer the majority of SCC mortality

These factors alone are often not specific enough to determine risk-appropriate treatment and further management

SCC treatment plans are guided by risk of metastasis

Risk-appropriate SCC management is ***limited by classification systems*** (NCCN, BWH, AJCC) with ***low positive predictive value*** (PPV)

NCCN=National Comprehensive Cancer Network; BWH = Brigham and Women's Hospital;
AJCC = American Joint Committee on Cancer

DecisionDx-SCC Informs Risk-Appropriate Management To Guide Patient Care

For high-risk ***SCC patients*** with one or more risk factors

9 peer-reviewed publications to date

Validated in ***420-patient cohort*** of high-risk SCC from 33 U.S. centers

~3,100 patients have been enrolled in studies to date from ***144 centers***

Utilizing ***existing sales channels***: dermatologists (including Mohs surgeons)

Incorporation of DecisionDx-SCC with traditional risk factors can ***improve patient classification*** compared to traditional risk factors alone

Comprehensive Diagnostic Offering Improves Clinically Actionable Reporting for ~99% of Concerning Lesions

Market Snapshot	Clinical Question	Clinical Utility	Transforming Disease Management
~$600M revenue opportunity[1] **~300k patients** with an indeterminate biopsy[2] *After melanoma diagnosis, clinicians can order DecisionDx-Melanoma using the same tissue sample*	Is the melanocytic lesion malignant or benign?	Leverages the strengths of myPath Melanoma and DecisionDx DiffDx-Melanoma for the benefit of patient care	Annually, ~300,000 difficult-to-diagnose lesions cannot be confidently diagnosed with a routine histopathology, leading to an ambiguous diagnosis or uncertain treatment plans[3,4]
		Designed to be used as an ***adjunct to histopathology*** when the distinction between a benign nevus and a malignant melanoma cannot be made confidently by histopathology alone	***Proven utility in reducing ambiguous diagnoses*** by dermatopathologists and ***reducing surgical re-excisions*** by dermatologists ***in patients with benign GEP results***[5,6,7]
		Adds diagnostic clarity and confidence for more informed patient care	***Improves clinically actionable reporting for ~99% of concerning lesions***[7]

[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 suspicious pigmented lesion biopsies estimated at 2,000,000 with addressable market limited to the 15% with an indeterminant biopsy
[3]Shoo et al. *J Am Acod Dermatol* 2010; [4]Lott et al. *JAMA Derm* 2018; [5]Cokerell et al. *Per Med* 2017; [6]Cockerell et al. *Medicine* 2016; [7]Farberg et al. *SKIN J Cutaneous* Med 2020; [8]Goldberg et al. *SKIN* 2021: s79;

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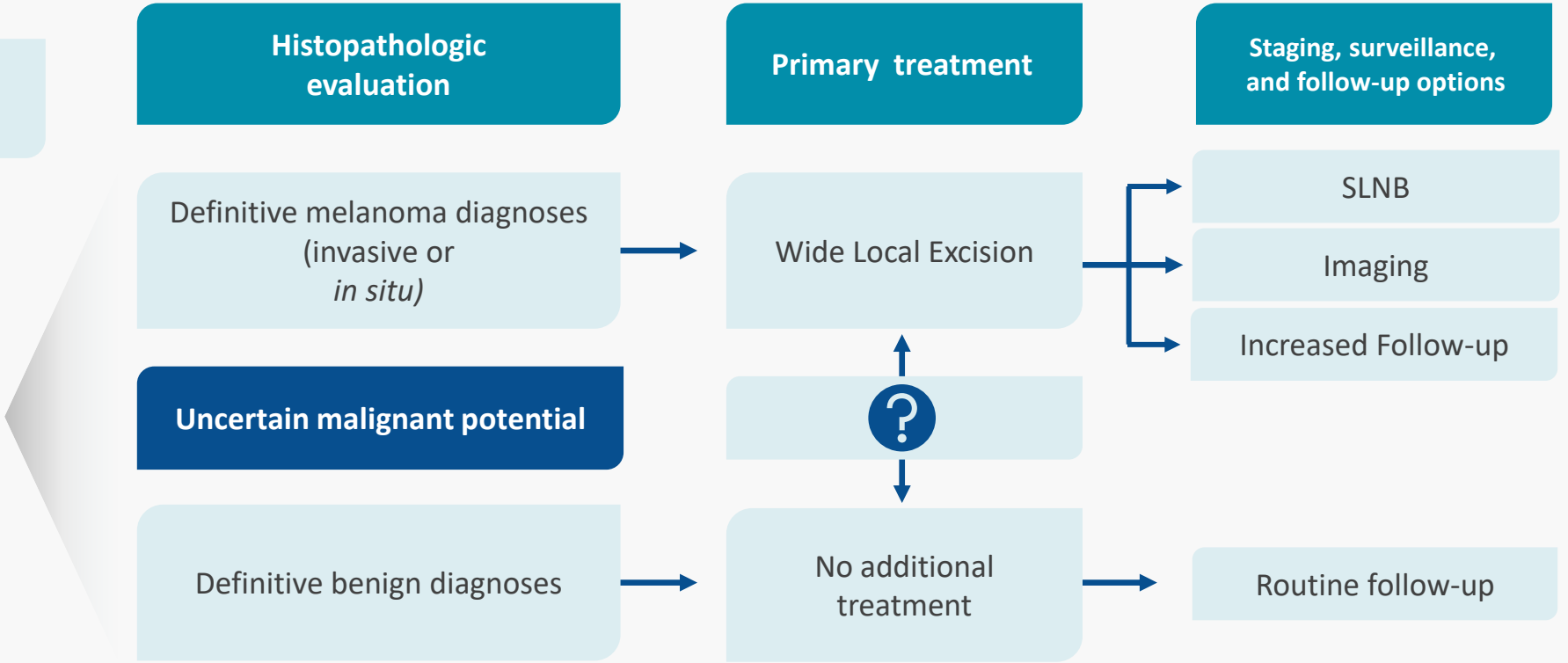
Diagnosing Melanoma, the Clinical Issue: Uncertainty Creates An Over- Or Under-Treatment Dilemma

Clinically evaluated suspicious pigmented lesions

~2 million melanocytic skin biopsies



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Inflammatory Pipeline Test

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
~20-30% of patients with PSO will go on to develop psoriatic arthritis, which can produce irreversible joint damage and significant patient morbidity

Systemic therapy guidance tools have the potential to streamline therapeutic interventions for patients and avoid ineffective, expensive medication courses

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Castle's Inflammatory Skin Disease Pipeline Test Is Being Developed To Predict Systemic Therapy Response

50
Committed Sites

50
Total Target Sites

4,800
Target Patient Enrollment

Program Milestones	Q2-Q32021	Q32021	Q22022	2025
	Steering committee formed with top KOLs	First patient enrolled	Proof of RNA extraction method concept	Target launch

As of 2/17/22

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Gastrointestinal

TissueCypher: Designed to Predict Future Development Of Esophageal Cancer In Patients With Barrett's Esophagus

Market Snapshot	Clinical Decision Point	Clinical Utility	Transforming Disease Management
~$1B revenue opportunity[1] **~384k patients** receiving upper GI endoscopies/year w/ confirmed Dx of BE[2]	Which BE patients will progress to HGD or esophageal cancer?	Provides a ***5-year individual risk of progression to high-grade dysplasia or esophageal adenocarcinoma*** for patients with confirmed BE	TissueCypher high risk score ***independently predicted an almost 8-fold increased risk of progression to esophageal cancer***[3]
		Identifies patients: 1) At risk for future progression and patients harboring prevalent HGD/cancer 2) At low risk of progression who may be able to avoid unnecessary treatment or surveillance	***Strongest predictor of progression to esophageal cancer (risk-stratification)*** TissueCypher hazard ratio of 7.7 compared to GI expert pathologist diagnosis of 3.9 ($p<0.0001$); pooled analysis[4-8]
			Clinical use study demonstrates ***55% change in patient management***[9]

HGD = high-grade dysplasia; EAC = esophageal adenocarcinoma; BE = Barrett's esophagus

[1]U.S. TAM = Total addressable market based on estimated patient population assuming average reimbursement rate among all payors.

[2]384,000 upper GI endoscopies/year with confirmed dx of BE (ND, IND, LGD) x $2,513 = U.S. only TAM of ~$1 billion

[3]Iyer, P, et. al. Prediction of Progression in Barrett's Esophagus Using a Tissue Systems Pathology Test: A Pooled Analysis of International Multicenter Studies. DDW 2021 Presentation (Manuscript Submitted)

[4]Critchley-Thorne, et. al. Cancer Epidemiol Biomarkers Prev. Jan 2016; [5]Critchley-Thorne, et. al. Cancer Epidemiol Biomarkers Prev. Feb 2017 [6]Davison, et. al. Am J Gastroenterol. Feb 2020

[7]Frei, et. al. Clin Transl Gastroenterol. Oct 2020; [8]Frei, et. al. Am J Gastroenterol. Apr 2021; [9]Diehl, et.al. Endoscopy International Open, 2021, Mar; 9(3): E348-E355

CASTLE BIOSCIENCES

Decision Dx-UM

The Standard of Care for Evaluating Metastatic Risk in Uveal Melanoma

DecisionDx-UM: The Standard Of Care In The Management Of Newly Diagnosed Uveal Melanoma

Strong Evidence Base

- 21 peer-reviewed publications, ***3,000+ patients***

Widespread adoption

- ***More than 90%*** of U.S. ocular oncology institutions order
- ***1,618 reports*** issued in 2021

Broad Reimbursement

- In 2021, received payment on ~93% of claims
- Medicare LCD ***covers patients*** with a confirmed diagnosis and no evidence of metastatic disease
- 2022 Medicare rate of $7,776

AJCC and NCCN Guideline Inclusion

Facts About Uveal Melanoma

~2,000 patients diagnosed in the U.S. annually

~97% of patients – no evidence of metastatic disease at the time of diagnosis

~30% will develop metastases within 5 years

DecisionDx-UM

15-Gene Expression Profile (GEP) Test

Low-risk: **~67%**
Low Intensity Management

High-risk: **~33%**
High Intensity Management

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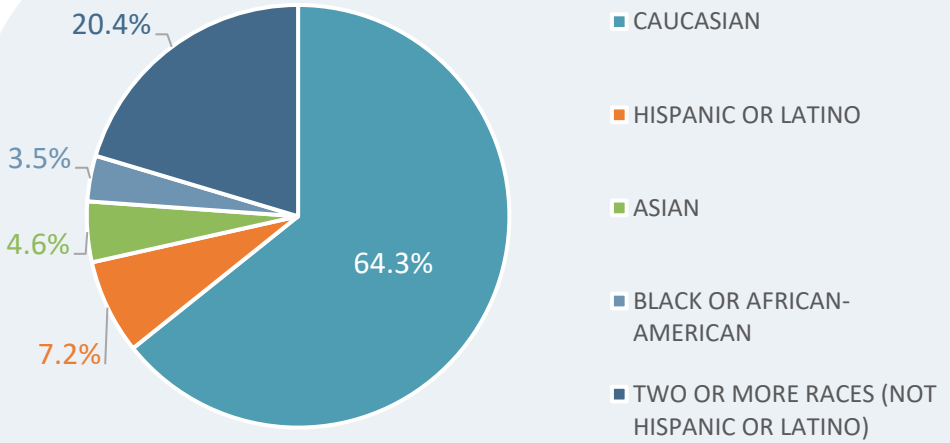
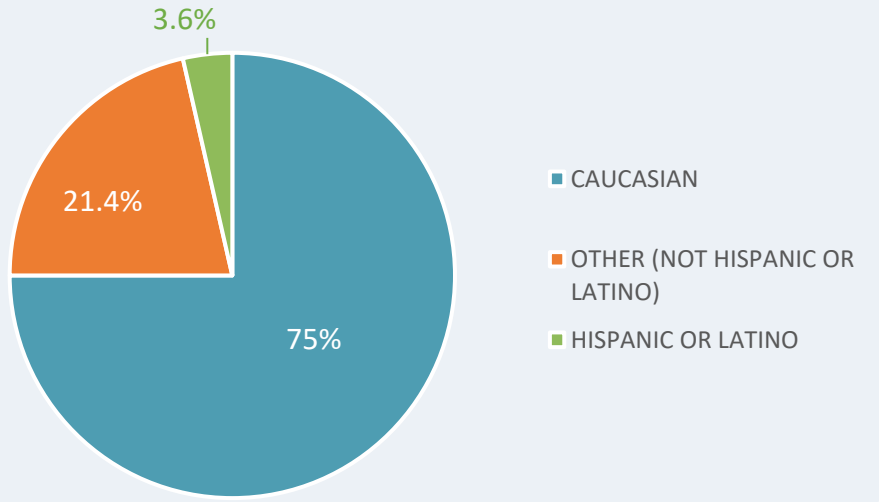
Commitment To Diversity

ETHNICITY/RACE

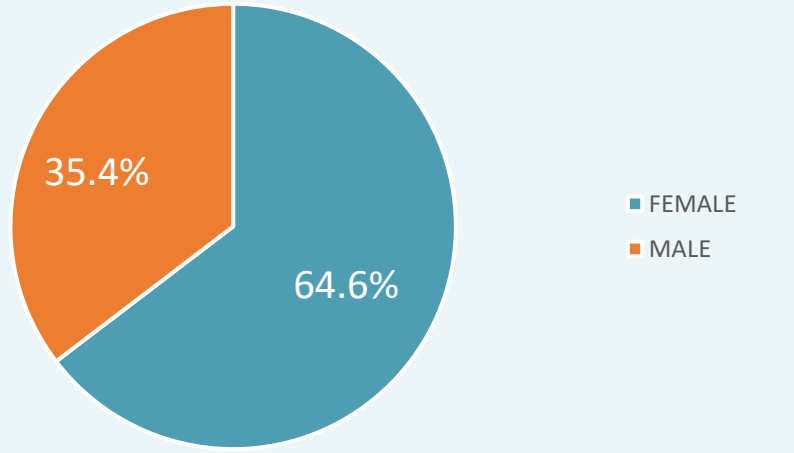
All Employees



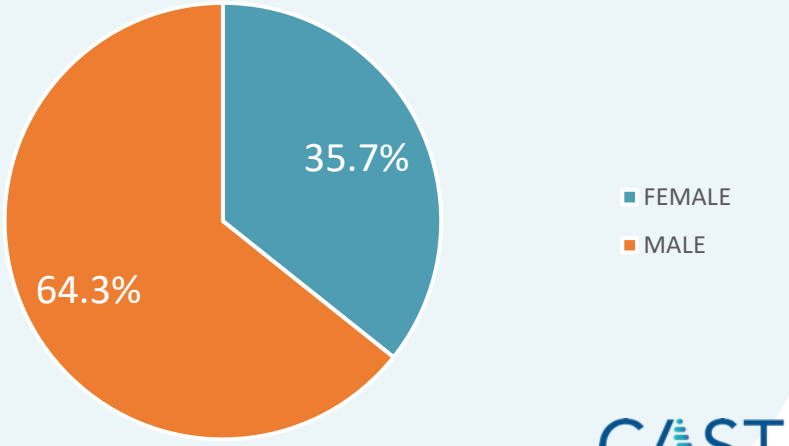
Executives



GENDER



TOTAL EMPLOYEES = 345



Data as of 12/31/21, Executive= Executive Director or Regional Business Director level and above

Award-Winning Company

Committed to cultivating a culture of innovation, continuous growth and advancement

TOP WORK PLACES 2021 HOUSTON CHRONICLE

TOP WORK PLACES 2022 USA

The Healthcare Technology Report

The Top 100 Healthcare Technology Companies of 2021

MEDTECH BREAKTHROUGH AWARD 2021

BEST NEW TECHNOLOGY SOLUTION - ONCOLOGY -

HOUSTON CHRONICLE CHRON 100 HOUSTON'S LEADING COMPANIES PRESENTED BY TEXASINC 2020

HOUSTON CHRONICLE CHRON 100 HOUSTON'S LEADING COMPANIES PRESENTED BY TEXASINC 2021

Inc. Best-Led Companies 2021

AMERICAN SKIN ASSOCIATION

2019 Technology Innovation in Melanoma Award Winner

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Castle Biosciences Is Improving Health Through Innovative Tests That Guide Patient Care

CUTANEOUS MELANOMA[1,2]

DecisionDx MELANOMA

PROGNOSTIC

Predicting Individual Risk of Recurrence or Metastasis in Stage I, II, and III Melanoma

myPath Melanoma DecisionDx DiffDx-Melanoma

DIAGNOSTIC

Highly Accurate and Objective Tests Characterizing Difficult-to-Diagnose Melanocytic Lesions

SQUAMOUS CELL CARCINOMA

DecisionDx-SCC

PROGNOSTIC

Better Identifies Risk of Metastasis in Patients with One or More Risk Factors

UVEAL MELANOMA[3]

DecisionDx-UM

PROGNOSTIC

The Standard of Care for Evaluating Metastatic Risk in Uveal Melanoma

BARRETT'S ESOPHAGUS[4]

tissuecypher BARRETT'S ESOPHAGUS ASSAY

PROGNOSTIC

Predicting Individual Risk of Progression to Esophageal Cancer in Barrett's Esophagus

[1]2022 CMS rate: DecisionDx-Melanoma, $7,193; [2]2022 CMS rate: myPath-Melanoma, $1,950
[3]2022 CMS rate: DecisionDx-UM, $7,776; [4]2022 CMS rate: TissueCypher BE, $2,513
https://www.cms.gov/medicaremedicare-fee-service-paymentclinicallabfeeschedclinical-laboratory-fee-schedule-files/22clabq1

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THANK YOU

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, 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 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 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 GAAP basis. 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.

Reconciliation Of Non-GAAP Financial Measures (Unaudited)

The table below presents the reconciliation of adjusted revenue and adjusted gross margin, which are non-GAAP measures. See "Use of Non-GAAP Financial Measures (UNAUDITED)" on the previous slide for further information regarding the Company's use of non-GAAP financial measures.

	Three Months Ended December 31,		Twelve Months Ended December 31,	
	2021	2020	2021	2020
(in thousands)				
Adjusted revenue				
Net revenues (GAAP)	$ 25,039	$ 17,299	$ 94,085	$ 62,649
Revenue associated with test reports delivered in prior periods	780	(3,515)	(3,324)	(176)
Adjusted revenue (Non-GAAP)	$ 25,819	$ 13,784	$ 90,761	$ 62,473
Adjusted gross margin				
Gross margin (GAAP)[1]	$ 19,434	$ 14,626	$ 76,305	$ 52,964
Amortization of acquired intangible assets	1,008	—	1,958	—
Revenue associated with test reports delivered in prior periods	780	(3,515)	(3,324)	(176)
Adjusted gross margin (Non-GAAP)	$ 21,222	$ 11,111	$ 74,939	$ 52,788
Gross margin percentage (GAAP)[2]	77.6 %	84.5 %	81.1 %	84.5 %
Adjusted gross margin percentage (Non-GAAP)[3]	82.2 %	80.6 %	82.6 %	84.5 %

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 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 measure. See "Use of Non-GAAP Financial Measures (UNAUDITED)" on the previous slide for further information regarding the Company's use of non-GAAP financial measures.

	Three Months Ended December 31,		Twelve Months Ended December 31,	
	2021	2020	2021	2020
(in thousands)				
Adjusted operating cash flow				
Net cash (used in) provided by operating activities (GAAP)	$ (2,781)	$ (430)	$ (18,983)	$ 9,865
Medicare advance payment[1]	2,999	—	8,350	(8,350)
HHS provider relief funds[2]	—	1,882	(1,882)	—
Adjusted operating cash flow (Non-GAAP)	$ 218	$ 1,452	$ (12,515)	$ 1,515

1. In April 2020, 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 is 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

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

BOARD OF DIRECTORS

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

Recent Achievements And Expected Future Milestones

✓ **Dec. 2018:** Initial LCD effective for DecisionDx-Melanoma

✓ **July 2019:** IPO

✓ **Dec 2019:** Expanded outside sales territories to 32

✓ **3Q2020:** Launch of DecisionDx-SCC

✓ **3Q2020:** Dermatologic commercial team expansion

✓ **4Q2020:** Launch of DiffDx-Melanoma

2021+: Continued evidence development for all commercialized products

2021+: Continued development of dermatologic pipeline products; potential launches in 2025

2Q2022: Potential draft LCD for DecisionDx-SCC and DecisionDx DiffDx-Melanoma

✓ **Feb. 2019:** Expanded outside sales territories to 23

✓ **Aug. 2019:** Expanded draft LCD for DecisionDx-Melanoma posted

✓ **Oct. 2020:** LCD expansion finalized for DecisionDx-Melanoma, effective date 12/6/20

✓ **2H2020:** Initiation of work on additional dermatology pipeline products

✓ **1H2021:** Dermatologic commercial team expansion to mid-60s

✓ **2021:** Acquired myPath® Melanoma

✓ **Dec. 2021:** Acquired Cernostics

✓ **Jan. 2022:** GI commercial team trained and in the field

2023: Potential effective LCD for DecisionDx-SCC and DecisionDx DiffDx-Melanoma

✓ = Achieved

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