CASTLE BIOSCIENCES

Transforming the management of dermatologic cancers

March 8, 2021

DISCLAIMERS

FORWARD-LOOKING STATEMENTS

The information in this presentation contains forward-looking statements and information 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, our anticipated milestones, including expected commercial availability of our pipeline products and revenue generation therefrom, estimated total addressable market attributable to our existing and pipeline products, the impact of our tests, including DecisionDx-Melanoma, DecisionDx-SCC and DecisionDx DiffDxMelanoma, including the effectiveness of integrating the i31-GEP algorithm into our DecisionDx-Melanoma test, our plans for commercial expansion, including anticipated growth of our sales team, our prospects and plans and the objectives of management. 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, the timing and amount of revenue we are able to recognize in a given fiscal period, unexpected delays in planned launch of our pipeline products, the level and availability of reimbursement for our products, our ability to manage our anticipated growth and the risks set forth in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2020, filed with the SEC on November 9, 2020, 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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LEADING DERMATOLOGIC DIAGNOSTICS COMPANY

TRANSFORMING THE MANAGEMENT OF SKIN CANCER

SUITE OF SKIN CANCER PROGNOSTIC AND DIAGNOSTIC TESTS

EXPANSIVE BODY OF EVIDENCE

STRONG FINANCIAL POSITION

ROBUST PIPELINE

CULTURE OF INNOVATION

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FINANCIAL SUMMARY 4Q AND YEAR-END 2020

	4Q20	4Q19	Twelve months ended 12/31/20	Twelve months ended 12/31/19
Revenue	**$17.3M**	$17.6M	**$62.6M**	$51.9M
Total GEP test reports[1]	**5,157**	4,914	**18,185**	17,055
Total Derm test reports[1]	**4,747**	4,480	**16,790**	15,529
Operating Cash Flow	**$(0.4)M**	$4.5M	**$9.9M**	$7.0M
Adj. Operating Cash Flow[2]	**$1.5M**	$4.5M	**$1.5M**	$7.0M
Gross Margin	**85%**	89%	**85%**	86%
Cash & Cash Equivalents			**$410M (as of 12/31/20)**	$99M (as of 12/31/19)

[1] Castle had two commercially available GEP tests in 2019.
[2]See Non-GAAP reconciliations at the end of this presentation.

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ESTIMATED ~$5.5B U.S. TOTAL ADDRESSABLE MARKET[1]
In market and pipeline tests, leveraging established dermatologic sales channels

Indication/ Test outcome	Trade Name	Reimbursement Status	Peer-Reviewed Publications	Primary Customers	Initial Launch Targets	Initial addressable market, patients[2]	Estimated U.S. TAM
Cutaneous melanoma/ Risk of metastasis	DecisionDx MELANOMA	MCR, MCRA Commercial – in process	28	Derms (including Mohs), Surgeons	—	***~130k patients*** classified as Stage I, II or III	~$540M
Cutaneous squamous cell carcinoma/ Risk of metastasis	DecisionDx-SCC	Expected draft LCD in 2021	4	Derms (including Mohs)	~4,300 current customers[3]	***~200k*** w/ high-risk features	~$820M
Suspicious pigmented lesions/ Melanoma status	DecisionDx DiffDx-Melanoma	Expected draft LCD in 2021	2	Dermpaths, Derms	~1,850 current dermpath customers[4]	***~300k patients*** w/indeterminant biopsy	~$600M
Pipeline Tests	Target launches anticipated by the end of 2025	N/A	N/A	Expected to utilize existing dermatologic sales channels	To be announced	To be announced	~$3.6B

[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 o r 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]Clinicians who ordered DecisionDx-Melanoma in LTM (as of 12/31/2020)
[4]Pathologists who provided clinical specimens for DecisionDx-Melanoma in LTM (as of 12/31/2020)
-MCR = Medicare. MCRA = Medicare Advantage; current customer estimates based on LTM.

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CASTLE'S LONG-TERM REVENUE GROWTH POTENTIAL

2021

DecisionDx MELANOMA
(Expanded LCD effective Dec 2020)

CUTANEOUS MELANOMA

2022

DecisionDx-SCC
DecisionDx DiffDx-Melanoma
(Potential LCDs effective in 2022)

DecisionDx MELANOMA

SQUAMOUS CELL CARCINOMA
CUTANEOUS MELANOMA

2025

Pipeline Expansion
(Expected launches ~2025)

DecisionDx-SCC
DecisionDx DiffDx-Melanoma

DecisionDx MELANOMA

ADDITIONAL TESTS FOR DERMATOLOGIC DISEASES

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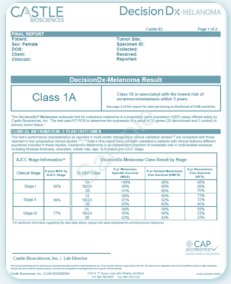
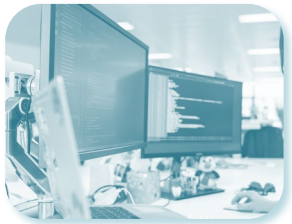
THE CASTLE APPROACH

Identify dermatologic diseases with high unmet medical need, where *genomic information* has the potential to *improve management decisions*

CAP-accredited, CLIA-certified commercial labs



Suite of skin cancer tests designed to provide clinicians with *precise, personalized* information, enabling more accurate treatment plan decisions



Leveraging *artificial intelligence,* tests are designed to provide *actionable information* based on tumor gene expression patterns

Test results inform management decisions within *nationally accepted* treatment *guidelines*

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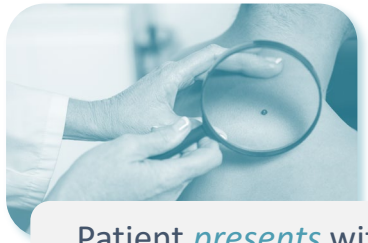
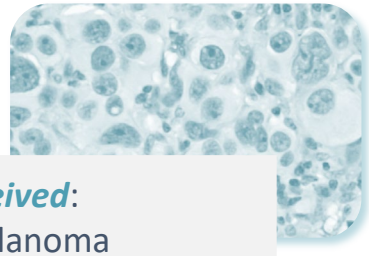
Decision Dx MELANOMA

Informing clinical decision making for patients with invasive melanoma

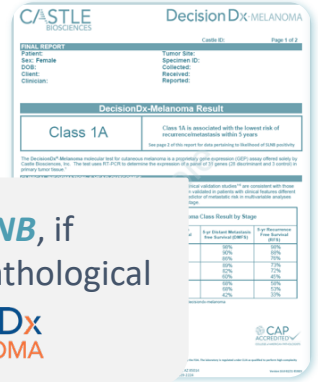
DECISIONDX-MELANOMA: AFTER DIAGNOSIS OF CANCER



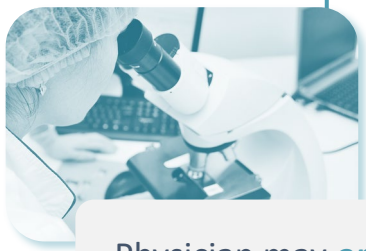
Patient *presents* with mole to PCP or dermatologist



Biopsy ***results received***:
- Positive for melanoma
- Negative
- Uncertain malignant potential



Physician may ***order SLNB***, if warranted per clinicopathological features and DecisionDx MELANOMA



Physician may ***order biopsy***

If melanoma, clinician orders DecisionDx MELANOMA to answer **SLNB** and/or **management questions:**
- Is the risk of SLN-positivity high enough to warrant referral for the SLNB surgery?
- What is the individual risk of recurrence?

Management ***plan determined, based on personalized risk***

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DECISIONDX-MELANOMA: AFTER DIAGNOSIS FOR MORE ACCURATE RISK ASSESSMENTS

Stage I – III melanoma diagnosis

DecisionDx MELANOMA

CM tumor tissue

RNA isolation

RT-PCR: cDNA generation and amplification, RT-PCR

qPCR: open array card, 31-gene expression profile

GEP analysis with a proprietary algorithm to predict class

Class 1A

Lowest risk of recurrence and/or metastasis within 5 years

Class 1B/2A

Increased risk of recurrence and/or metastasis within 5 years

Class 2B

Highest risk of recurrence and/or metastasis within 5 years

Gerami et al. *Clin Cancer Res* 2015; Gerami et al. *JAAD* 2015; Zager et al. *BMC Cancer* 2018; Gastman et al. *JAAD* 2019

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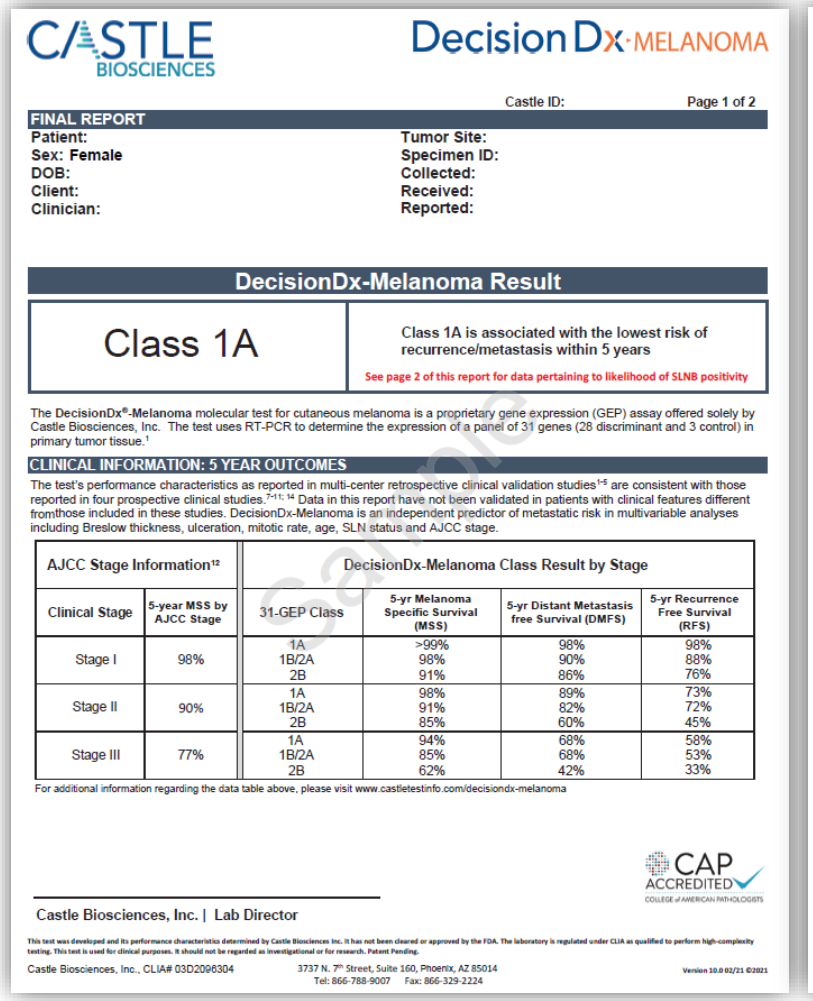
INTEGRATED TEST RESULT
i31-GEP utilizes artificial intelligence designed to provide a more precise prediction of SLN positivity risk



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Castle ID: Page 1 of 2

FINAL REPORT

Patient:	**Tumor Site:**
Sex: Female	**Specimen ID:**
DOB:	**Collected:**
Client:	**Received:**
Clinician:	**Reported:**

DecisionDx-Melanoma Result

Class 1A	Class 1A is associated with the lowest risk of recurrence/metastasis within 5 years See page 2 of this report for data pertaining to likelihood of SLNB positivity

The **DecisionDx®-Melanoma** molecular test for cutaneous melanoma is a proprietary gene expression (GEP) assay offered solely by Castle Biosciences, Inc. The test uses RT-PCR to determine the expression of a panel of 31 genes (28 discriminant and 3 control) in primary tumor tissue.[1]

CLINICAL INFORMATION: 5 YEAR OUTCOMES

The test's performance characteristics as reported in multi-center retrospective clinical validation studies[1-5] are consistent with those reported in four prospective clinical studies.[7-11; 14] Data in this report have not been validated in patients with clinical features different fromthose included in these studies. DecisionDx-Melanoma is an independent predictor of metastatic risk in multivariable analyses including Breslow thickness, ulceration, mitotic rate, age, SLN status and AJCC stage.

AJCC Stage Information[12]		DecisionDx-Melanoma Class Result by Stage			
Clinical Stage	5-year MSS by AJCC Stage	31-GEP Class	5-yr Melanoma Specific Survival (MSS)	5-yr Distant Metastasis free Survival (DMFS)	5-yr Recurrence Free Survival (RFS)
Stage I	98%	1A	>99%	98%	98%
		1B/2A	98%	90%	88%
		2B	91%	86%	76%
Stage II	90%	1A	98%	89%	73%
		1B/2A	91%	82%	72%
		2B	85%	60%	45%
Stage III	77%	1A	94%	68%	58%
		1B/2A	85%	68%	53%
		2B	62%	42%	33%

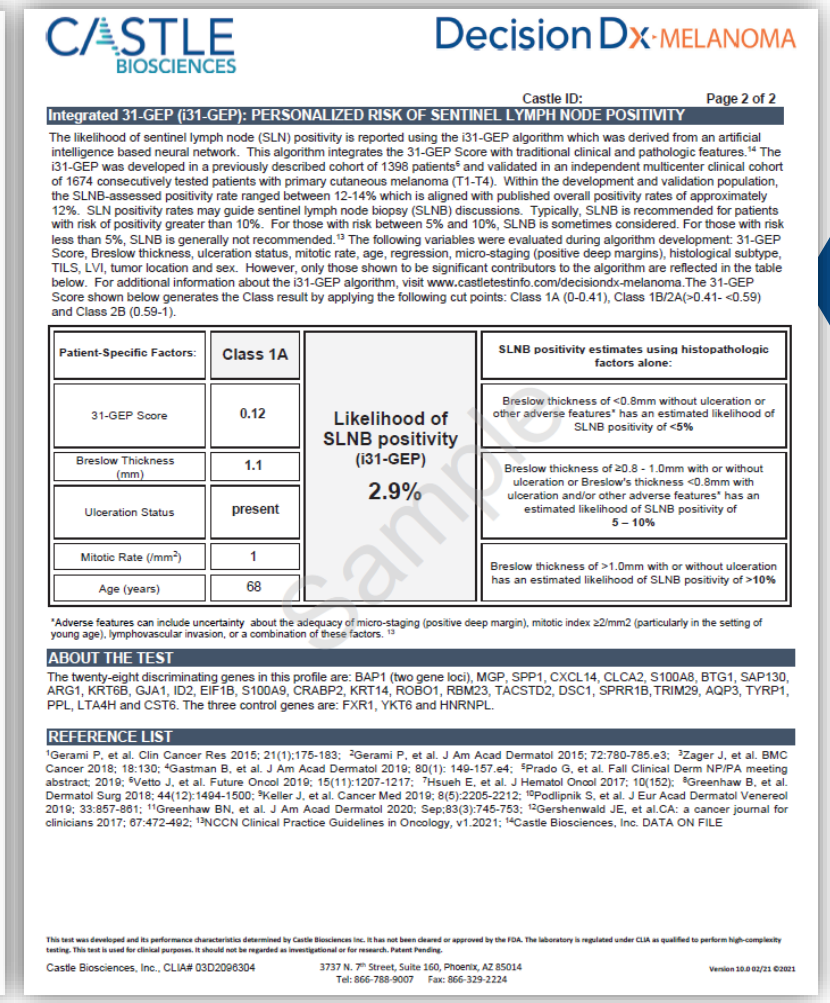
For additional information regarding the data table above, please visit www.castletestinfo.com/decisiondx-melanoma

CAP ACCREDITED — COLLEGE of AMERICAN PATHOLOGISTS

Castle Biosciences, Inc. | Lab Director

This test was developed and its performance characteristics determined by Castle Biosciences Inc. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. Patent Pending.

Castle Biosciences, Inc., CLIA# 03D2096304 — 3737 N. 7th Street, Suite 160, Phoenix, AZ 85014 — Tel: 866-788-9007 Fax: 866-329-2224 — Version 10.0 02/21 ©2021



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Integrated 31-GEP (i31-GEP): PERSONALIZED RISK OF SENTINEL LYMPH NODE POSITIVITY

The likelihood of sentinel lymph node (SLN) positivity is reported using the i31-GEP algorithm which was derived from an artificial intelligence based neural network. This algorithm integrates the 31-GEP Score with traditional clinical and pathologic features.[14] The i31-GEP was developed in a previously described cohort of 1398 patients[6] and validated in an independent multicenter clinical cohort of 1674 consecutively tested patients with primary cutaneous melanoma (T1-T4). Within the development and validation population, the SLNB-assessed positivity rate ranged between 12-14% which is aligned with published overall positivity rates of approximately 12%. SLN positivity rates may guide sentinel lymph node biopsy (SLNB) discussions. Typically, SLNB is recommended for patients with risk of positivity greater than 10%. For those with risk between 5% and 10%, SLNB is sometimes considered. For those with risk less than 5%, SLNB is generally not recommended.[13] The following variables were evaluated during algorithm development: 31-GEP Score, Breslow thickness, ulceration status, mitotic rate, age, regression, micro-staging (positive deep margins), histological subtype, TILS, LVI, tumor location and sex. However, only those shown to be significant contributors to the algorithm are reflected in the table below. For additional information about the i31-GEP algorithm, visit www.castletestinfo.com/decisiondx-melanoma.The 31-GEP Score shown below generates the Class result by applying the following cut points: Class 1A (0-0.41), Class 1B/2A(>0.41- <0.59) and Class 2B (0.59-1).

Patient-Specific Factors:	Class 1A	Likelihood of SLNB positivity (i31-GEP) 2.9%	SLNB positivity estimates using histopathologic factors alone:
31-GEP Score	0.12		Breslow thickness of <0.8mm without ulceration or other adverse features* has an estimated likelihood of SLNB positivity of **<5%**
Breslow Thickness (mm)	1.1		Breslow thickness of ≥0.8 - 1.0mm with or without ulceration or Breslow's thickness <0.8mm with ulceration and/or other adverse features* has an estimated likelihood of SLNB positivity of **5 – 10%**
Ulceration Status	present		
Mitotic Rate (/mm²)	1		Breslow thickness of >1.0mm with or without ulceration has an estimated likelihood of SLNB positivity of **>10%**
Age (years)	68		

*Adverse features can include uncertainty about the adequacy of micro-staging (positive deep margin), mitotic index ≥2/mm2 (particularly in the setting of young age), lymphovascular invasion, or a combination of these factors. [13]

ABOUT THE TEST

The twenty-eight discriminating genes in this profile are: BAP1 (two gene loci), MGP, SPP1, CXCL14, CLCA2, S100A8, BTG1, SAP130, ARG1, KRT6B, GJA1, ID2, EIF1B, S100A9, CRABP2, KRT14, ROBO1, RBM23, TACSTD2, DSC1, SPRR1B,TRIM29, AQP3, TYRP1, PPL, LTA4H and CST6. The three control genes are: FXR1, YKT6 and HNRNPL.

REFERENCE LIST

[1]Gerami P, et al. Clin Cancer Res 2015; 21(1):175-183; [2]Gerami P, et al. J Am Acad Dermatol 2015; 72:780-785.e3; [3]Zager J, et al. BMC Cancer 2018; 18:130; [4]Gastman B, et al. J Am Acad Dermatol 2019; 80(1): 149-157.e4; [5]Prado G, et al. Fall Clinical Derm NP/PA meeting abstract; 2019; [6]Vetto J, et al. Future Oncol 2019; 15(11):1207-1217; [7]Hsueh E, et al. J Hematol Oncol 2017; 10(152); [8]Greenhaw B, et al. Dermatol Surg 2018; 44(12):1494-1500; [9]Keller J, et al. Cancer Med 2019; 8(5):2205-2212; [10]Podlipnik S, et al. J Eur Acad Dermatol Venereol 2019; 33:857-861; [11]Greenhaw BN, et al. J Am Acad Dermatol 2020; Sep;83(3):745-753; [12]Gershenwald JE, et al.CA: a cancer journal for clinicians 2017; 67:472-492; [13]NCCN Clinical Practice Guidelines in Oncology, v1.2021; [14]Castle Biosciences, Inc. DATA ON FILE

This test was developed and its performance characteristics determined by Castle Biosciences Inc. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. Patent Pending.

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The new Integrated Test Result incorporates traditional clinicopathologic factors with the DecisionDx-Melanoma continuous score designed to provide a precise, personalized likelihood of sentinel lymph node positivity

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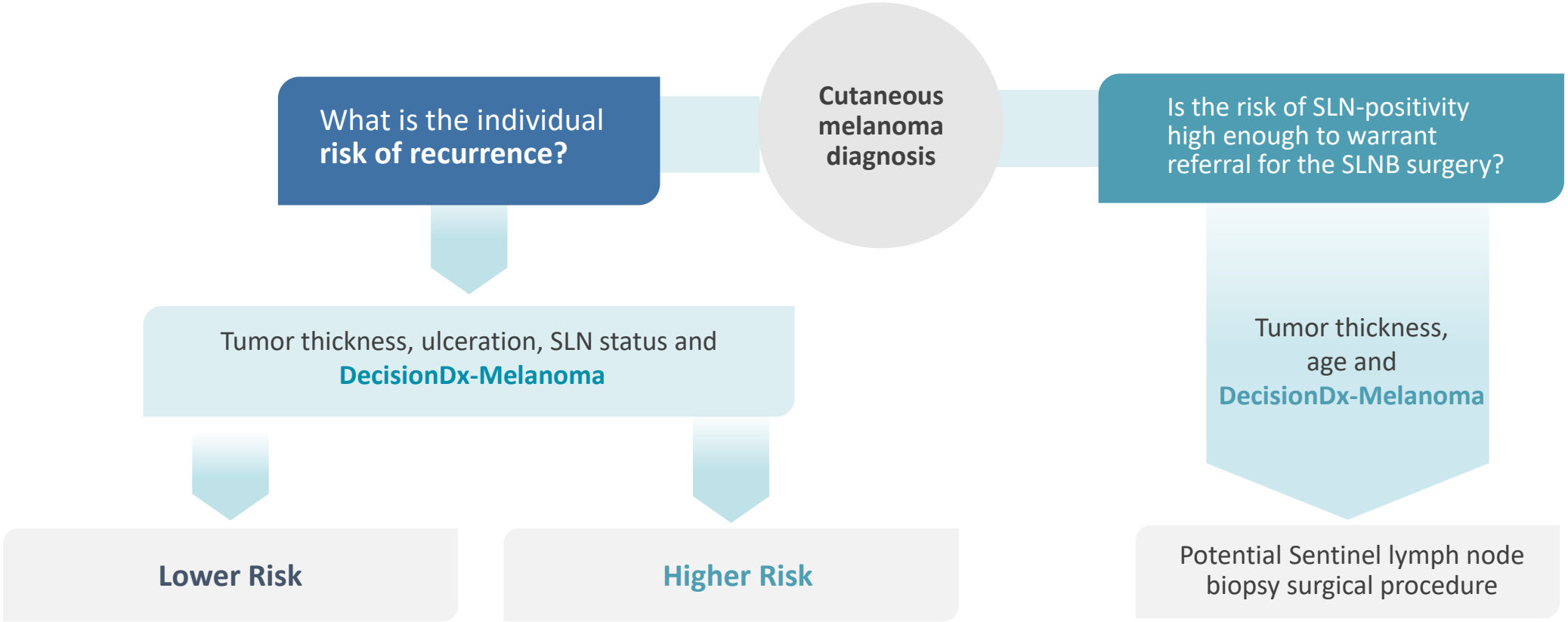
AFTER DIAGNOSIS, TWO CLINICAL QUESTIONS HELP GUIDE MELANOMA MANAGEMENT

CHOOSING RISK-APPROPRIATE LEVEL OF MANAGEMENT IS KEY



SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy. Source: NCCN Guidelines for Cutaneous Melanoma v3.2020

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DECISIONDX-MELANOMA INFORMS BOTH RISK ASSESSMENTS, NOW WITH i31-GEP TO PREDICT SLN POSITIVITY RISK

NEW i31-GEP algorithm
Risk of ***existing metastasis to SLN***

For SLNB eligible patients with:

- T1a with adverse features
- T1b-T4

i31-GEP algorithm integrates test score with clinicopathologic factors for precise and personalized risk

31-GEP continuous score

+

Breslow Thickness
Ulceration
Mitotic rate
Age

DecisionDx-Melanoma informs ***use of SLNB***

Risk of ***recurrence***

For patients with:

- T ≥0.3 mm

Class 1A: lowest risk

Class 1B/2A: increased risk

Class 2B: highest risk

DecisionDx-Melanoma ***informs management*** (clinical follow-up, referrals, imaging, adjuvant therapy)

Vetto et al. Future Oncol 2019; Marks et al SKIN J Cutaneous Med 2019

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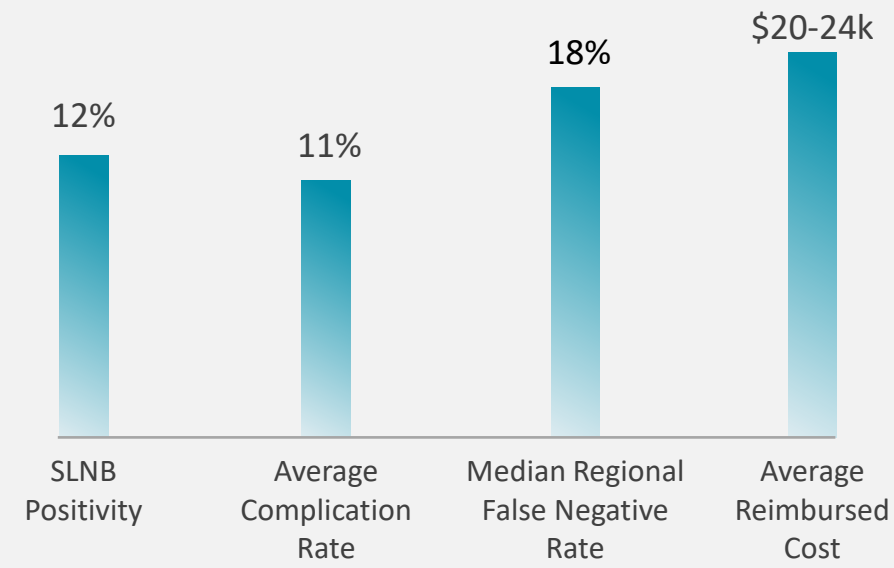
DECISIONDX-MELANOMA
STRATIFIES RISK OF POSITIVE SLN TO INFORM DISCUSSIONS

Objective: right treatment, right patient, right time

SLNB: risky, poor prognostic tool

- 88% SLNB recipients negative
- Anesthesia risks, surgical complications: 11% [1]
- False negative: 5% - 21%[3]
- No survival benefit, low sensitivity:
  - 2/3 of melanoma deaths were SLN-negative [2]

LIMITATIONS OF CURRENT STAGING TO INFORM SLNB SURGERY



Text sources:
[1]Systematic review of 21 articles representing 9,047 patients (Moody *Eur J Sur Onc* 2016); [2]Morton *NEJM* 2014; [3]False negative rate definition limited to metastasis to the regional lymphatics, not to distant metastasis or death. Median false negative rate = 17.6%; [3]Sondak & Zager *Ann Surg Oncol* 2010

Graph sources:
- SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy. MCR=Medicare Cost Report.
- Source: AJCC v7 *J Clin Oncol* 2009; SEER data release 2017; Morton et al. *N Engl J Med* 2014; Whiteman et al. *J Invest Dermatol* 2015; Shaikh et al. *J Natl Cancer Inst* 2016; Poklepovic and Carvajal. *Oncology* 2018; Sondak and Zager. *Ann Surg Oncol* 2010. Moody et al. *Euro Jrnl Surg Onc* 2017.

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SOLUTION 1: DECISIONDX-MELANOMA INFORMS SLNB SURGERY DISCUSSIONS IN T1a – T4 MELANOMAS

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DecisionDx-MELANOMA

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Integrated 31-GEP (i31-GEP): PERSONALIZED RISK OF SENTINEL LYMPH NODE POSITIVITY

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Patient-Specific Factors:	Class 2B	Likelihood of SLNB positivity (i31-GEP)	SLNB positivity estimates using histopathologic factors alone:
31-GEP Score	0.82	15.1%	Breslow thickness of <0.8mm without ulceration or other adverse features* has an estimated likelihood of SLNB positivity of **<5%**
Breslow Thickness (mm)	0.7		Breslow thickness of ≥0.8 - 1.0mm with or without ulceration or Breslow's thickness <0.8mm with ulceration and/or other adverse features* has an estimated likelihood of SLNB positivity of **5 – 10%**
Ulceration Status	absent		
Mitotic Rate (/mm²)	0		Breslow thickness of >1.0mm with or without ulceration has an estimated likelihood of SLNB positivity of **>10%**
Age (years)	66		

*Adverse features can include uncertainty about the adequacy of micro-staging (positive deep margin), mitotic index ≥2/mm2 (particularly in the setting of young age), lymphovascular invasion, or a combination of these factors. [13]

I31-GEP is designed to take patients from population-based risk to more precise, personalized risk to guide SLNB discussions

DecisionDx-Melanoma could result in 74% fewer SLNB surgeries, potentially saving U.S. healthcare system $250M[1,3]

[1]Vetto et al. *Future Oncol* 2019. [2]Hsueh et al. Poster discussion abstract, ASCO 2019. [3]Clearview health economic model, data on file.
T1-T2 tumors are ≤2.0mm thick ("Breslow's" thickness or depth). MSS = melanoma specific survival. OS = overall survival. DMFS = distant metastasis free survival. RFS = recurrence free survival. n/r = not reported.

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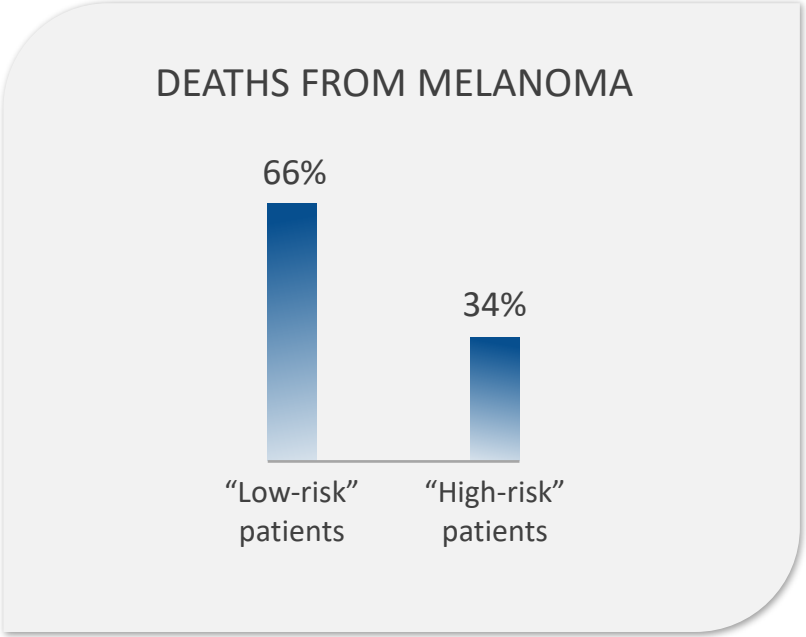
PROBLEM 2: UNDER-MANAGEMENT EVIDENT IN MELANOMA

CURRENT RISK ASSESSMENTS MISS PATIENTS WITH AGGRESSIVE TUMOR BIOLOGY

Early detection, lower tumor burden associated with better therapy responses, survival outcomes[1-5]

Appropriate surveillance, including imaging of high-risk patients, is critical[1-5]

AJCC clinicopathologic factors are helpful clinically, but majority of deaths occur in patients diagnosed with early-stage disease[6-8]



Prognostic accuracy must improve to determine the most appropriate melanoma management strategy for each patient

Text sources:[1]Poklepovic and Carvajal. *ONCOLOGY* 2018; [2]Ribas et al. *JAMA* 2016; [3]Schadendorf et al. *Eur J Can* 2017; [4]Robert et al. *J Clin Oncol* 2017; [5]Joseph et al. *Clin Cancer Res* 2018; [6]SEER data release 2017; [7]Whiteman et al. *J Invest Dermatol* 2015; [8]Shaikh et al. *J Natl Cancer Inst* 2016

Graph sources: AJCC v7 *J Clin Oncol* 2009; SEER data release 2017; Morton et al. *N Engl J Med* 2014; Whiteman et al. *J Invest Dermatol* 2015; Shaikh et al. *J Natl Cancer Inst* 2016; Poklepovic and Carvajal. *Oncology* 2018; Sondak and Zager. *Ann Surg Oncol* 2010. Moody et al. *Euro Jrnl Surg Onc* 2017.

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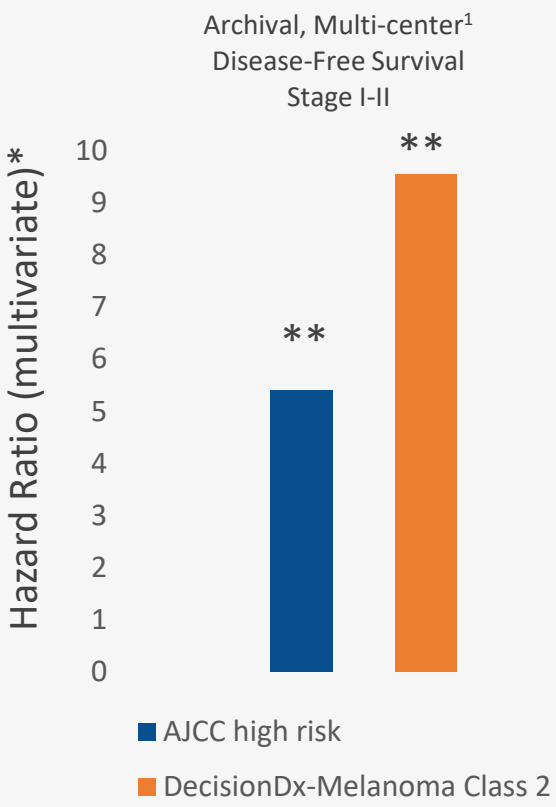
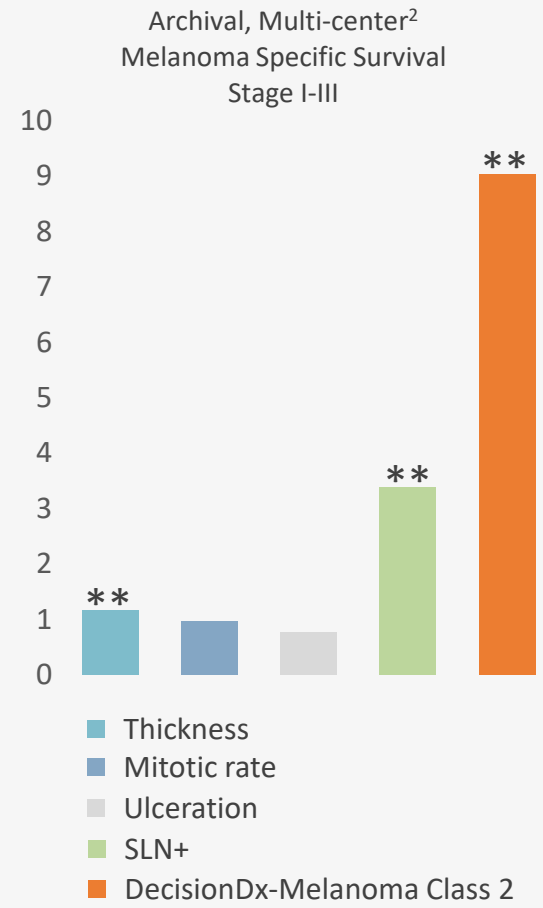
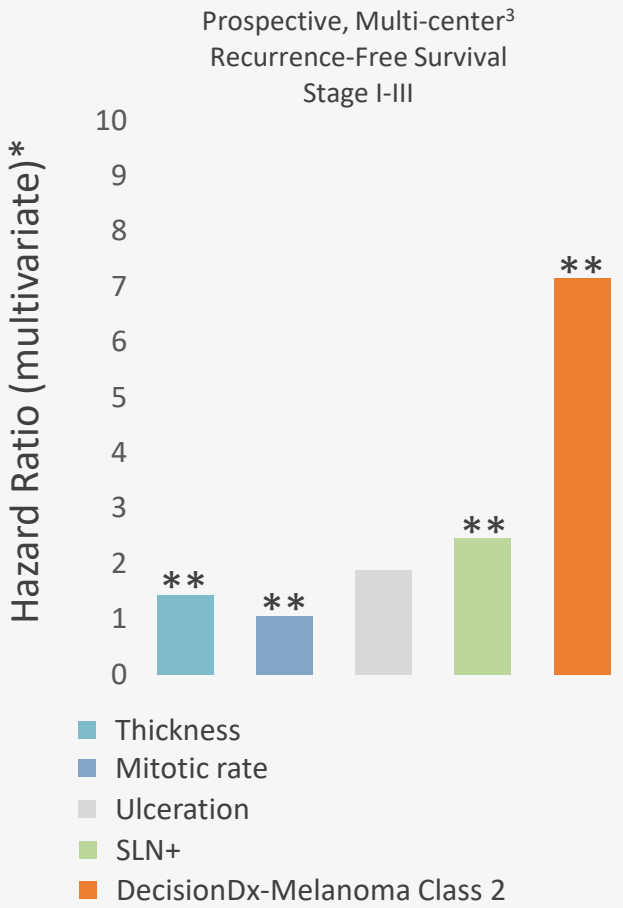
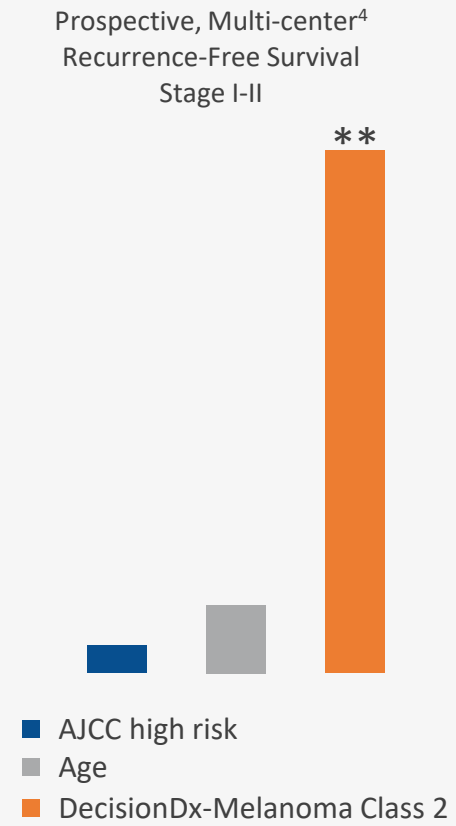
SOLUTION 2: DECISIONDX-MELANOMA IS A SIGNIFICANT, INDEPENDENT PREDICTOR OF OUTCOMES







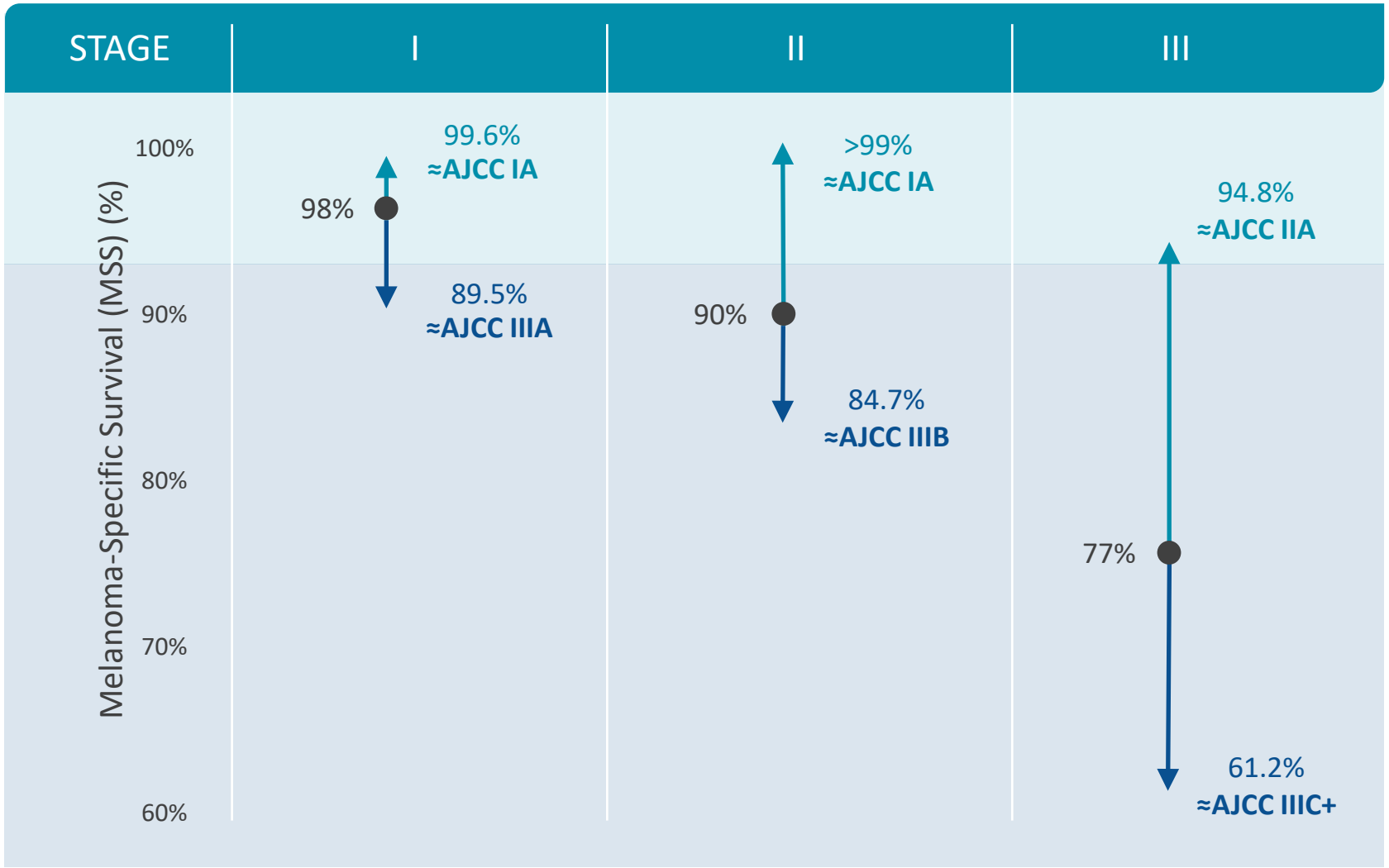


*Hazard ratio is continuous for thickness, categorical for other endpoints; **Statistically significant Data shown are from the first and most recent publications for archival and prospective studies

[1]Gerami et al. *Clin Cancer Res* 2015. [2]Gastman et al. *Jrnl Amer Acad Dermatol* 2019. [3]Hsueh et al. *Jrnl Hematol Oncol* 2017. [4]Podlipnik et al. *Jrnl Eur Asso Veneral and Derm* 2019.

CASTLE BIOSCIENCES

DECISIONDX-MELANOMA FURTHER STRATIFIES RISK OF RECURRENCE BEYOND AJCC (8TH Ed.) STAGING



NCCN Risk Category

Low Risk
Stage I-IIA

High Risk
Stage IIB-III

- **AJCC MSS**
- **Castle Class 1A MSS**
- **Castle Class 2B MSS**

Prado et al. *SKIN J Cutan Med* 2018:suppl 2. n=690

CASTLE BIOSCIENCES

SOLUTION 2: DECISIONDX-MELANOMA CHANGED MANAGEMENT FOR 50% OF PATIENTS

4 consecutive clinical impact studies:
47-53% change in ***risk-of-recurrence-based management***

Changes in patient management include:

- Imaging and labs
- Sentinel lymph node biopsy guidance
- Clinical visit frequency
- Referrals

Study	Design	# of Patients	% Change in Management
Berger[1]	Prospectively tested cohort, multi-center. Retrospective pre-test / post-test management.	156	**53%**
Dillon[2]	Prospective, multi-center: pre-test / post-test management	247	**49%**
Farberg[3]	169 physician impact study: patient vignettes with pre-test / post-test management	n/a	**47-50%**
Schuitevoerder[4]	Prospectively tested cohort, single center. Retrospective pre-test / post-test management; modeling of prospective cohort	91	**52%**

[1]Berger, et al. 2016 Curr Med Res Opin; [2]Dillon et al. 2018 Skin; [3]Farberg et al. 2017 Jrnl Drugs Derm; [4]Schuitevoerder, et al. 2018 Jrnl Drugs Derm.

CASTLE BIOSCIENCES

DECISIONDX-MELANOMA: WELL-STUDIED, INFORMS CANCER MANAGEMENT DECISIONS

>7,700

Patients included in studies including ***independent validation***

28

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

68,000+

Patients with a ***DecisionDx-Melanoma*** order from over ***6,800 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

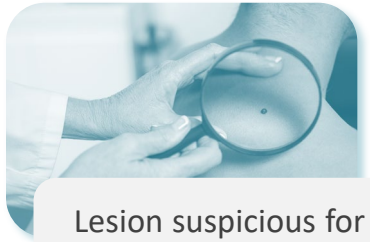
*ACCORDING TO SORT SYSTEM, USED BY AAD

CASTLE BIOSCIENCES

Decision Dx-SCC

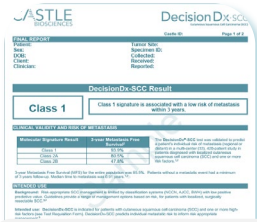
Identifying the risk of metastasis in patients with cutaneous squamous cell carcinoma with one or more risk factors

PATIENT JOURNEY: WHERE DECISIONDX-SCC FITS



Lesion suspicious for skin cancer **discovered** by patient or PCP

Diagnosis of SCC with≥1 risk factor



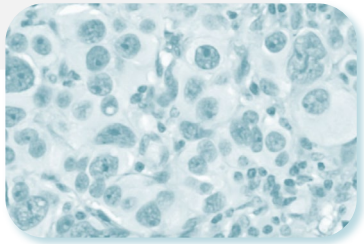
Test results **received** for DecisionDx-SCC

Patient referred to a dermatologist who performs a skin exam

History and physical

- Complete skin exam
- Regional lymph node exam

Skin biopsy



Order **placed** for DecisionDx-SCC

Treatment plan defined

- Curettage and electrodesiccation
- Standard excision
- Excision with wide margins
- Mohs

PROBLEM: 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 ***currently 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

CASTLE BIOSCIENCES

DESIGNED TO PREDICT INDIVIDUAL METASTATIC RISK TO INFORM RISK-APPROPRIATE MANAGEMENT

DecisionDx-SCC

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

200,000 high-risk patients annually;

$820M U.S TAM[1]

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

4 ***peer-reviewed publications*** to date;

Over ***1,400 patients*** enrolled in studies to date from ***92 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

[1] based on Castle estimates

CASTLE BIOSCIENCES

WORKFLOW FOR DECISIONDX-SCC: PROCESS IDENTICAL TO DECISIONDX-MELANOMA

Patient diagnosed with SCC and one or more risk factors

SCC tumor tissue

RNA isolation

RT-PCR: cDNA generation and amplification

qPCR: open array card
34 discriminant gene targets and 6 control genes

Analysis of GEP with a proprietary algorithm to determine Class and metastatic risk

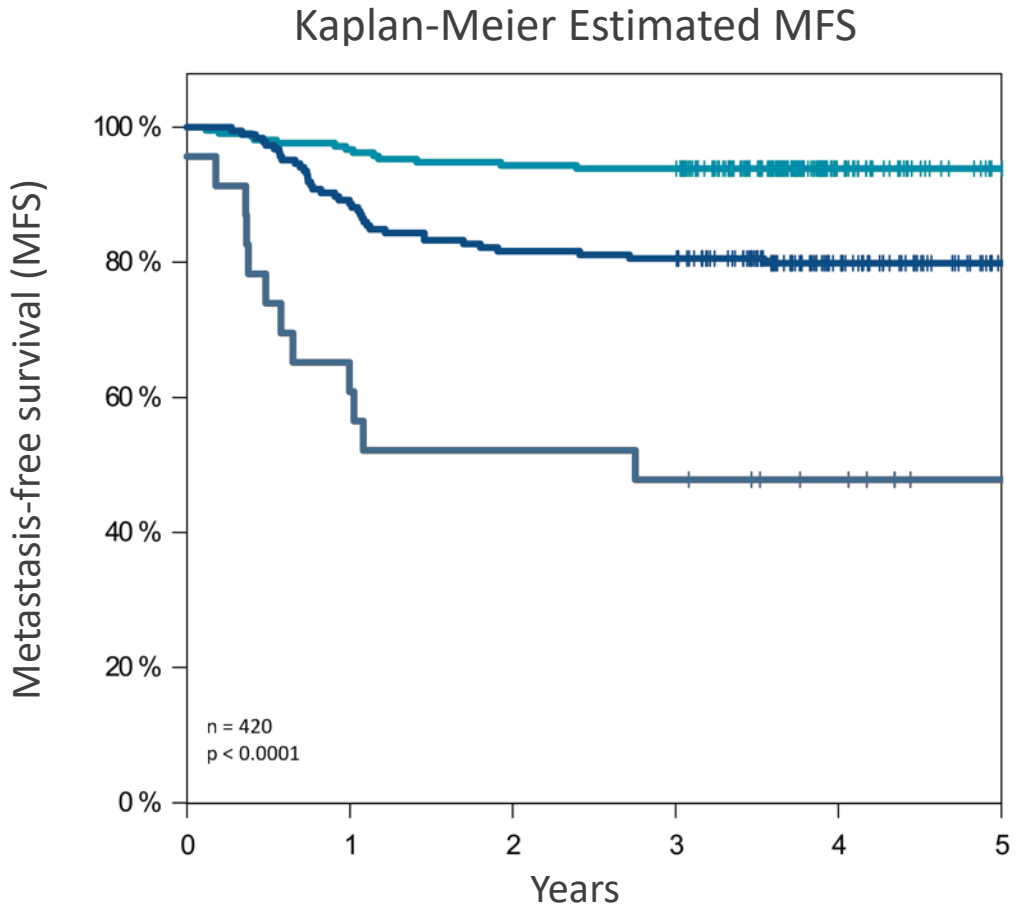
	Treatment plans may include	Follow-up plans may include
Class 1 low metastatic risk (~50% of results)a	• Surgery, if feasible • Clinical nodal exam	• Clinical follow-up: 1-2x per year • Clinical nodal exam
Class 2A moderate metastatic risk (~40% of results)	• Surgery, if feasible • Consider nodal imaging / staging • Consider oncology referral	• Clinical follow-up: 2-4x per year for 3 years • Baseline and annual nodal US/CT for 2 years
Class 2B high metastatic risk (<10% of results)	• Surgery, if feasible • Nodal imaging / staging • Consultation: radiation oncology • Consultation: medical oncology	• Clinical follow-up: 4-12x per year for 3 years • Baseline and 4x per year nodal US/CT for 2 years

DecisionDx-SCC results can inform management decisions within established guidelines

Wysong et al. *JAAD* 2020; Data on file, Castle Biosciences
NCCN Guidelines for Squamous Cell Skin Cancer v1.2020, 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

CASTLE BIOSCIENCES

DECISIONDX-SCC IS VALIDATED TO PREDICT METASTATIC RISK FOR INDIVIDUAL SCC PATIENTS WITH ONE OR MORE RISK FACTORS



Class 1 – Low Biological Risk

Less than half the general study population risk

Class 2A – Moderate Biological Risk

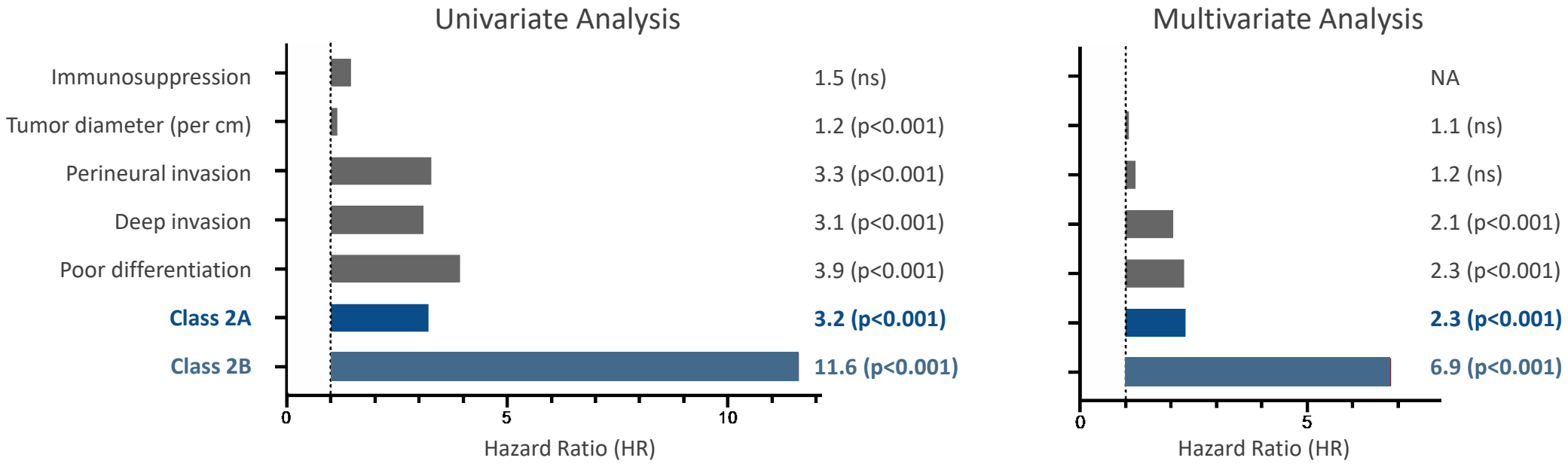
Similar to the strongest traditional factors

Class 2B – High Biological Risk

≥50% risk of metastasis

Wysong et al. *JAAD* 2020; Ibrahim et al. submitted; Data on file, Castle Biosciences.

CLASS 2A AND CLASS 2B ARE INDEPENDENT PREDICTORS OF METASTASIS



What is the impact of DecisionDx-SCC?

An SCC with deep invasion is ***2.1x more likely*** to ***metastasize*** than without.

Adding a Class 2A results shifts that to ***4.8x more likely*** to ***metastasize.***

Adding a Class 2B result shifts that to ***14.5x more likely*** to ***metastasize.***

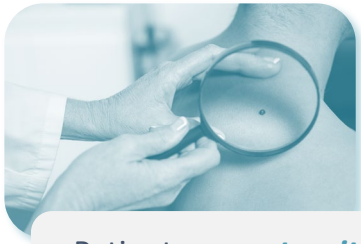
Deep invasion: beyond subcutaneous fat, depth >6mm, or Clark level V.
Wysong et al. *JAAD* 2020; Ibrahim et al. submitted; Data on file, Castle Biosciences.

CASTLE BIOSCIENCES

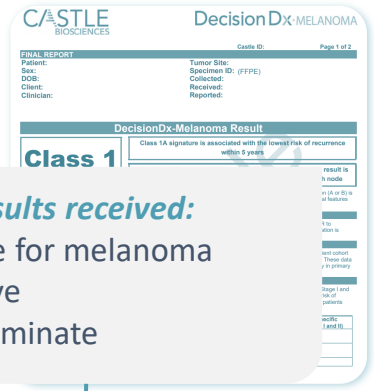
DecisionDx DiffDx·Melanoma

A highly accurate and objective test for melanocytic lesions of unknown malignant potential

DERMATOPATHOLOGISTS AND DERMATOLOGISTS WORK TOGETHER TO DIAGNOSE MELANOMA



Patient ***presents with mole*** to PCP or dermatologist



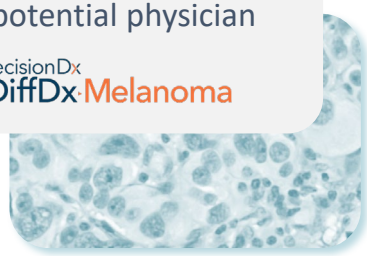
Biopsy ***results received:***

- Positive for melanoma
- Negative
- Indeterminate

Melanoma Diagnosis confirmed; physician can initiate management plan with DecisionDx MELANOMA

Physician may order ***biopsy***

If biopsy results show *uncertain malignant* potential physician orders DecisionDx DiffDx·Melanoma

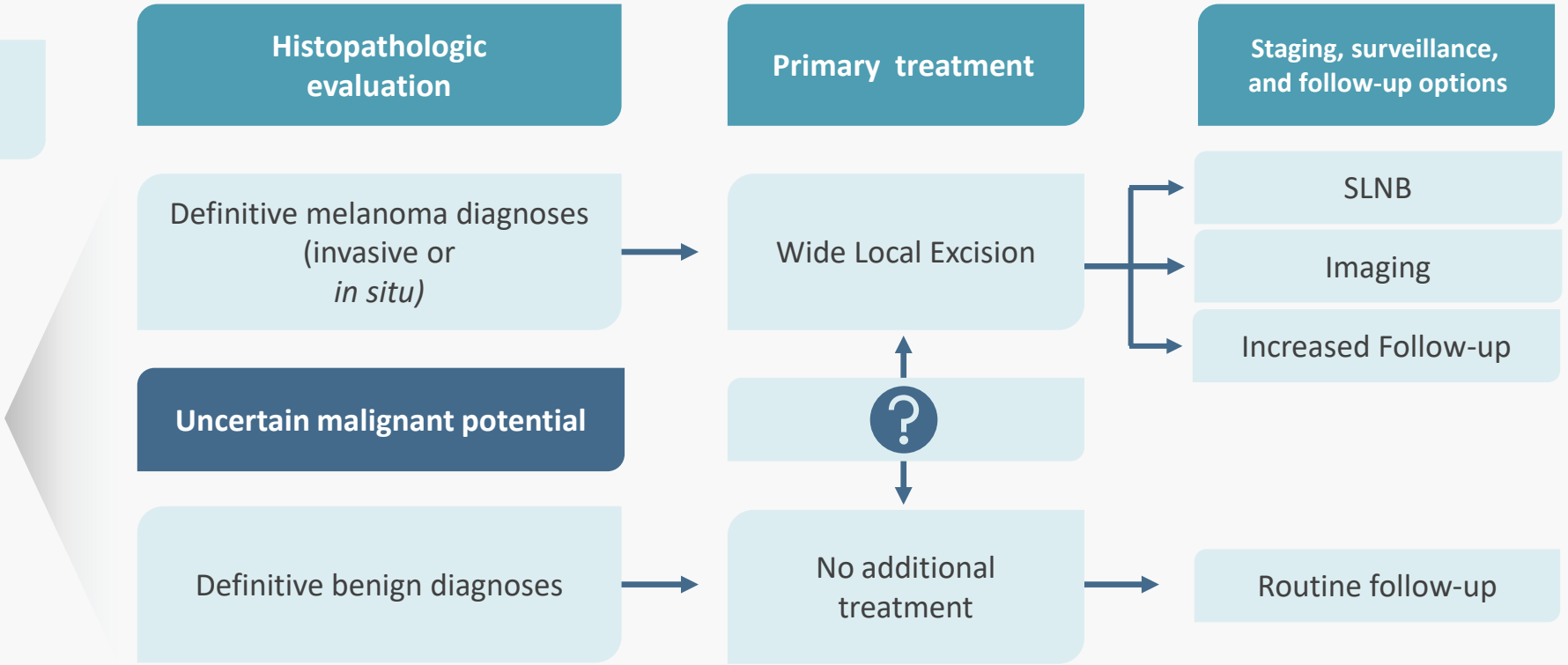


CASTLE BIOSCIENCES

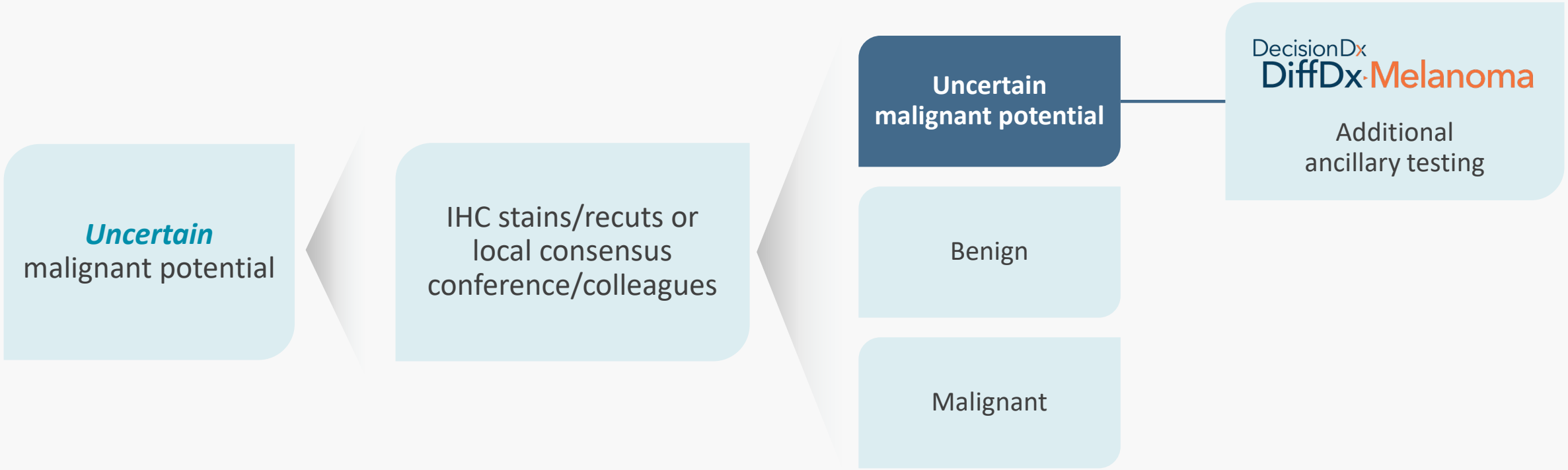
THE CLINICAL ISSUE: UNCERTAINTY CREATES AN OVER- OR UNDER-TREATMENT DILEMMA

Clinically evaluated suspicious pigmented lesions

~2 million melanocytic skin biopsies



DECISIONDX DIFFDX-MELANOMA IS DESIGNED FOR USE FOLLOWING IMMUNOHISTOCHEMISTRY (IHC) AND/OR LOCAL CONSENSUS



CASTLE BIOSCIENCES

WORKFLOW FOR DECISIONDX DIFFDX-MELANOMA:

PROCESS IDENTICAL TO DECISIONDX-MELANOMA

Diagnostically challenging pigmented (melanocytic) lesion

DecisionDx DiffDx-Melanoma

Dermatopathologist
OR
Dermatology clinician orders

FFPE tissue

RNA isolation — RT

cDNA generation and amplification

- Open array card ***32 discriminant*** gene targets and ***3 control*** genes

qPCR

Analysis of GEP with a proprietary AI algorithm to determine risk

Benign
Suggestive of benign neoplasm

Intermediate-Risk
Cannot exclude malignancy

Malignant
Suggestive of melanoma

DECISIONDX DIFFDX-MELANOMA: DESIGNED AND VALIDATED TO IMPROVE DIAGNOSTIC RESOLUTION FOR THE BENEFIT OF PATIENT CARE

	All ages N=503		Age > 65 years N=178	
	DecisionDx DiffDx-Melanoma	95% CI	DecisionDx DiffDx-Melanoma	95% CI
Sensitivity	99.1%	97.9-100	99.2%	97.6-100
Specificity	94.3%	91.5-97.1	100%	100-100
PPV	93.6%	90.5-96.7	100%	100-100
NPV	99.2%	98.1-100	98.1%	94.3-100
Intermediate-risk result	3.6%		3.4%	
Technical success rate	***96%***			

Samples that fall in intermediate-risk zone were excluded from the calculation.

PPV – positive predictive value; NPV – negative predictive value; CI – confidence interval.

Estrada et al. (2020) *SKIN J Cutan Med*

CASTLE BIOSCIENCES

IMPROVING DIAGNOSTIC RESOLUTION FOR THE BENEFIT OF PATIENT CARE

DecisionDx DiffDx-Melanoma

A definitive result from DecisionDx-DiffDx-Melanoma in ***≥96% of lesions*** submitted for testing

Includes ***multiple subtypes*** of lesions with uncertain malignant potential

Technical ***success*** rate of ***96%***

5-7 day turn around time/ similar to other ancillary tests

After melanoma diagnosis, clinicians can order DecisionDx-Melanoma; ***uses same tissue block***

Interpreted in the context of other clinical, laboratory and histopathologic information, DecisionDx DiffDx-Melanoma is designed to ***add diagnostic clarity*** and ***confidence*** for dermatopathologists, while ***helping dermatologists*** better ***understand the clinical implications*** for more informed patient care

Estrada et al. (2020) *J Cut Med SKIN*

CASTLE BIOSCIENCES

Decision Dx·UM

The Standard of Care for Evaluating Metastatic Risk in Uveal Melanoma

DecisionDx-UM : STANDARD OF CARE

Strong Evidence Base

- 17 peer-reviewed publications, ***2,000+ patients***

Widespread adoption

- ***90%+*** of U.S. ocular oncology institutions order
- ***1,395 reports*** issued in 2020

Broad Coverage

- ***156+ million*** total lives covered
- Medicare LCD ***covers patients*** with a confirmed diagnosis and no evidence of metastatic disease
- "Existing ADLT" ***status effective*** May 2019
- 2021 Medicare rate of ~$7700

AJCC and NCCN Guideline Inclusion

Uveal Melanoma – A Rare Eye Cancer

~1,600 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 3 years

DecisionDx-UM

(Uveal Melanoma)

15-Gene Expression Profile (GEP) Test

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

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

CASTLE BIOSCIENCES

MARKET AND FINANCIAL OVERVIEW

ESTIMATED ~$5.5B U.S. TOTAL ADDRESSABLE MARKET[1]
In market and pipeline tests, leveraging established dermatologic sales channels

Indication/ Test outcome	Trade Name	Reimbursement Status	Peer-Reviewed Publications	Primary Customers	Initial Launch Targets	Initial addressable market, patients[2]	Estimated U.S. TAM
Cutaneous melanoma/ Risk of metastasis	DecisionDx MELANOMA	MCR, MCRA Commercial – in process	28	Derms (including Mohs), Surgeons	—	***~130k patients*** classified as Stage I, II or III	~$540M
Cutaneous squamous cell carcinoma/ Risk of metastasis	DecisionDx-SCC	Expected draft LCD in 2021	4	Derms (including Mohs)	~4,300 current customers[3]	***~200k*** w/ high-risk features	~$820M
Suspicious pigmented lesions/ Melanoma status	DecisionDx DiffDx-Melanoma	Expected draft LCD in 2021	2	Dermpaths, Derms	~1,850 current dermpath customers[4]	***~300k patients*** w/indeterminant biopsy	~$600M
Pipeline Tests	Target launches anticipated by the end of 2025	N/A	N/A	Expected to utilize existing dermatologic sales channels	To be announced	To be announced	~$3.6B

[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 o r 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]Clinicians who ordered DecisionDx-Melanoma in LTM (as of 12/31/2020)
[4]Pathologists who provided clinical specimens for DecisionDx-Melanoma in LTM (as of 12/31/2020)
-MCR = Medicare. MCRA = Medicare Advantage; current customer estimates based on LTM.

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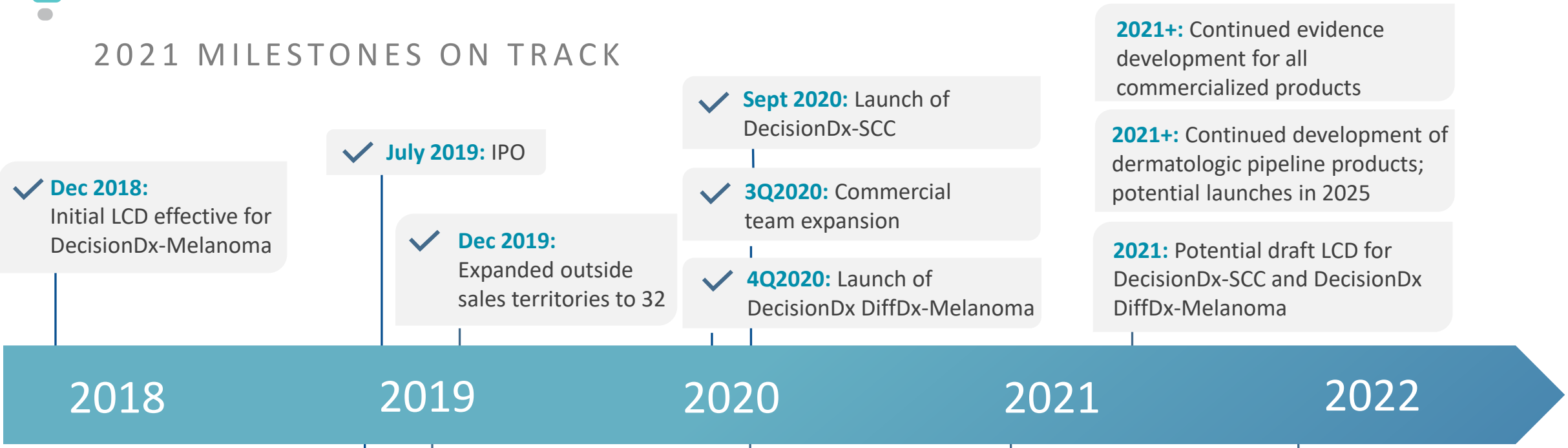
RECENT ACHIEVEMENTS AND EXPECTED FUTURE MILESTONES

2021 MILESTONES ON TRACK



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

✓ **July 2019:** IPO

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

✓ **Sept 2020:** Launch of DecisionDx-SCC

✓ **3Q2020:** Commercial team expansion

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

2021+: Continued evidence development for all commercialized products

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

2021: 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: Planned commercial team expansion to ~60

2021: Planned announcement of pipeline indications

2022: Potential effective LCD for DecisionDx-SCC and DecisionDx DiffDx-Melanoma

✓ = Achieved

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FACTORS DRIVING NEAR-AND LONG-TERM GROWTH

REVENUE

Test Report Volume
- Commercial sales team expansion in 1H21 to ~60

Reimbursement
- Strong ASP growth
- DecisionDx-Melanoma $7,193 PAMA rate through 2021
- DecisionDx-UM $7,776 PAMA rate through 2021

PROFITABILITY

Gross Margins
- 85% in 2020
- Continued margin expansion of existing products (increasing ASPs and efficiencies of scale) could be slightly offset by uptake of pipeline products ahead of reimbursement

PIPELINE

New Product Development
- Launched two skin cancer tests in 2020 with estimated $1.4B+ U.S. TAM
- Leverage of our existing skin cancer sales channels to support new products
- Initiated new pipeline products in dermatologic diseases with high unmet need; potential to launch 3-5 new tests by the end of 2025

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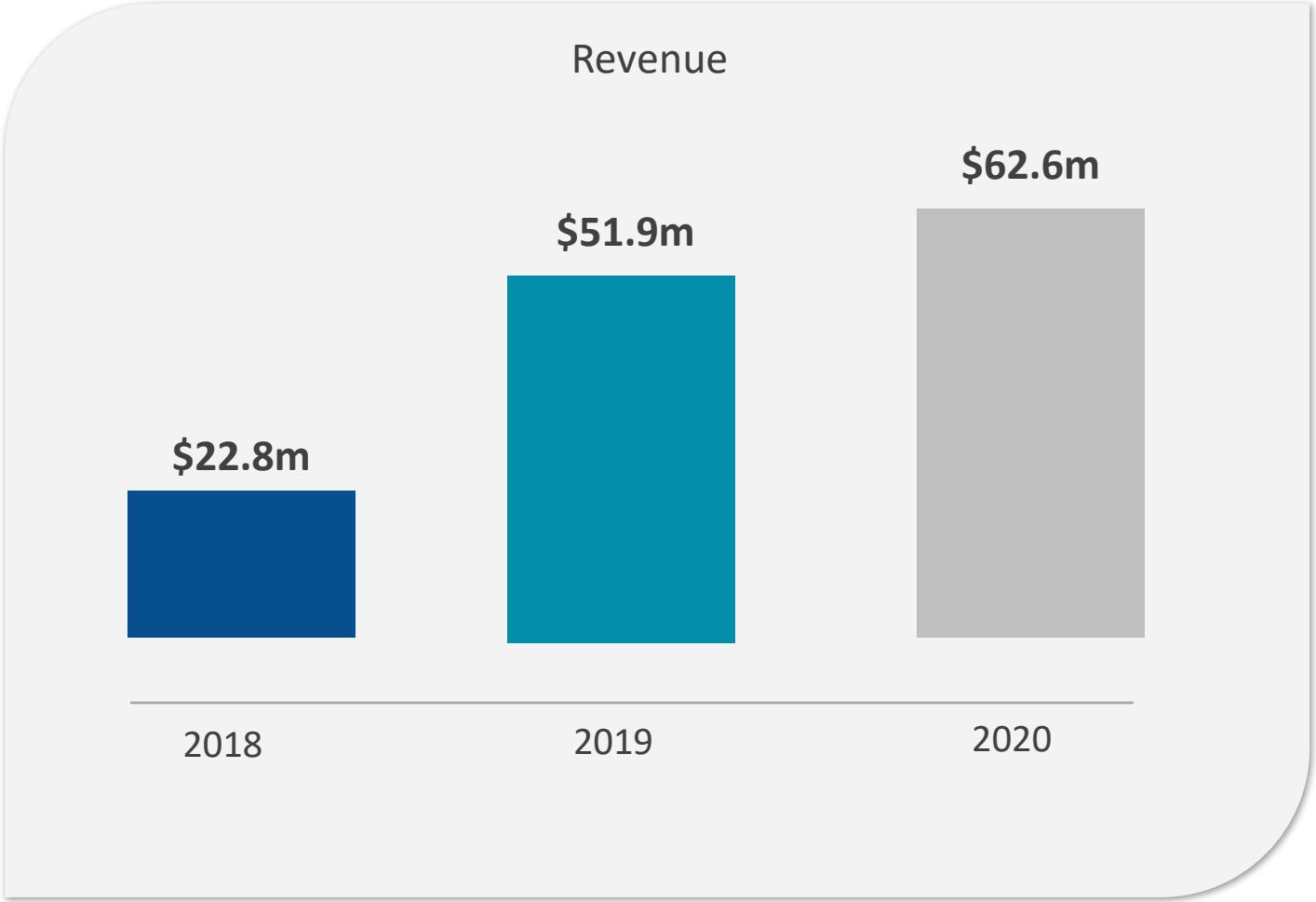
CONTINUED REVENUE GROWTH, DRIVEN BY TEST REPORT AND ASP GROWTH*



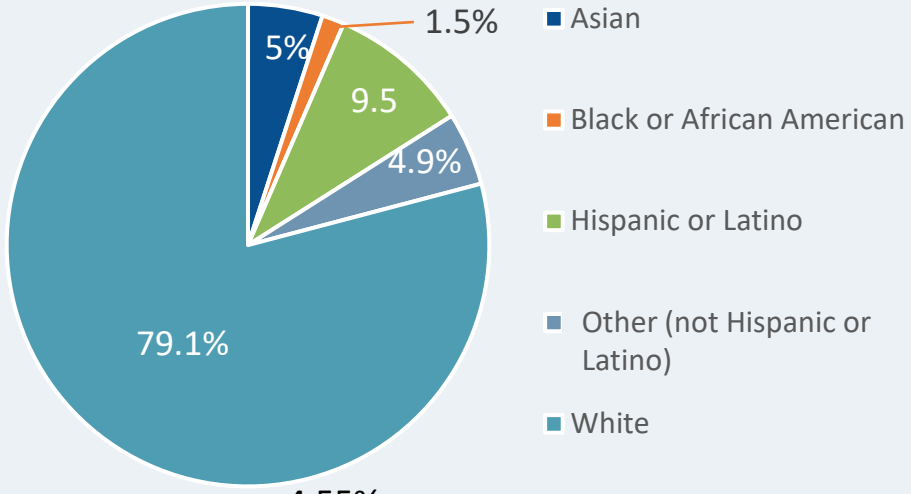
*2020 ASP growth over 2019 and 2018

CASTLE BIOSCIENCES

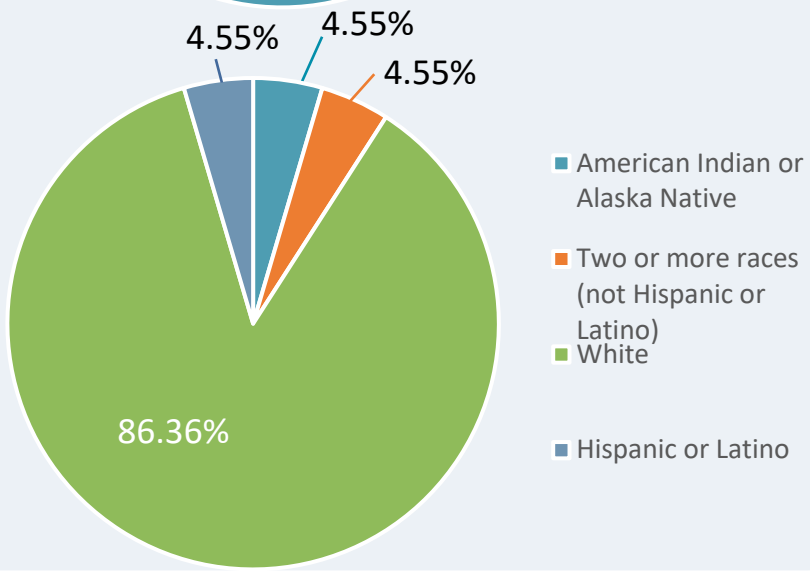
COMMITMENT TO DIVERSITY

ETHNICITY/RACE

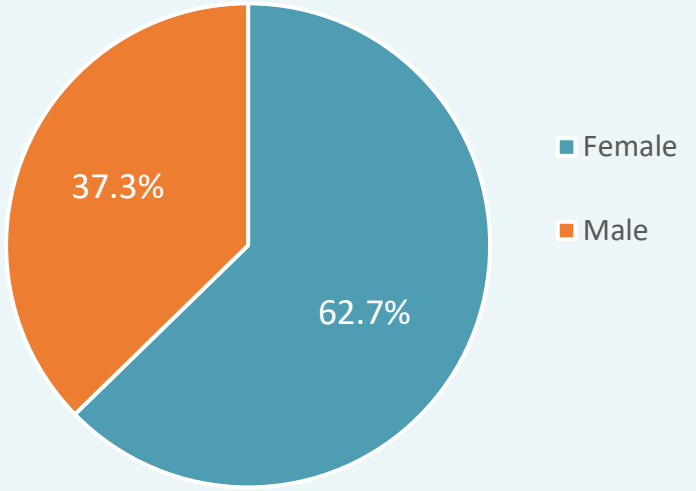
All Employees

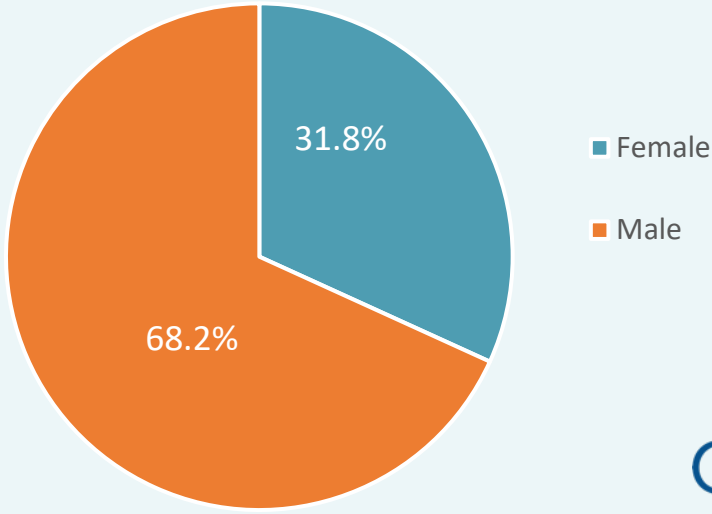


Executives



GENDER





Data as of 12/31/20, Executive= Executive Director or Regional Business Director level and above

LEADING DERMATOLOGIC DIAGNOSTICS COMPANY

TRANSFORMING THE MANAGEMENT OF SKIN CANCER

SUITE OF SKIN CANCER PROGNOSTIC AND DIAGNOSTIC TESTS

EXPANSIVE BODY OF EVIDENCE

STRONG FINANCIAL POSITION

ROBUST PIPELINE

CULTURE OF INNOVATION

CASTLE BIOSCIENCES

CASTLE BIOSCIENCES

THANK YOU

USE OF NON-GAAP FINANCIAL MEASURES (UNAUDITED)

- In this presentation, we use the metric of Adjusted Operating Cash Flow, which is a non-GAAP financial measure and is not calculated in accordance with generally accepted accounting principles in the United States (GAAP). This non-GAAP financial measure reflects adjustments to net cash provided by operating activities to remove the effects of two payments we received associated with government aid to healthcare providers due to COVID-19, which we believe are not indicative of our ongoing operations.

- We use Adjusted Operating Cash Flow internally because we believe this metric provides useful supplemental information in assessing our cash flow performance from our core ongoing business activities by removing the effects of these items on our operating cash flows. We believe this metric is also useful to investors as a supplement to GAAP measures in analyzing the performance of our business. However, this non-GAAP financial measure 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. This non-GAAP financial measure is not meant to be a substitute for net cash 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 this non-GAAP financial measure to the most directly comparable GAAP financial measure are presented on the next slide.

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

	Three Months Ended December 31,		Twelve Months Ended December 31,	
	2020	2019	2020	2019
(in thousands)				
Adjusted operating cash flow				
Net cash (used in) provided by operating activities (GAAP)	$ (430)	$ 4,493	$ 9,865	$ 7,015
Medicare advance payment[1]	—	—	(8,350)	—
HHS provider relief funds[2]	1,882	—	—	—
Adjusted operating cash flow (Non-GAAP)	$ 1,452	$ 4,493	$ 1,515	$ 7,015

1. In April 2020, we received an advance payment of $8.3 million from the Centers for Medicare & Medicaid Service (CMS), which will be applied against future Medicare claims that we submit for reimbursement beginning in April 2021. Originally, recoupment was to begin in August 2020, but recent legislation amended the recoupment schedule such that recoupment will begin in April 2021 and continue for a period of up to 17 months. 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 future claims are submitted for reimbursement and applied against this balance, we expect to include the advance payment in adjusted operating cash flow to the extent that Medicare claims submitted for reimbursement have been applied to the balance.

2. Reflects cash activity in the three months ended December 31, 2020 associated with the HHS provider relief funds.

CASTLE BIOSCIENCES

APPENDIX

LEADERSHIP TEAM OVERVIEW

MANAGEMENT TEAM

Derek Maetzold
Founder, Director, President and CEO

Frank Stokes
Chief Financial Officer

Bernhard Spiess
Chief Business Officer

Toby Juvenal
Chief Commercial Officer

Kristen Oelschlager, RN, CHC
Chief Operations Officer

Robert Cook, PhD
Senior Vice President, Research & Development

BOARD OF DIRECTORS

- Dan Bradbury
- Derek Maetzold
- Mara Aspinall
- Brad Cole
- Joe Cook, III
- Miles D. Harrison
- David Kabakoff