Transforming Disease Management
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; our expectations regarding timelines and milestones for our dermatologic, gastrointestinal and mental health franchises; our three-year projections for revenue, adjusted gross margins, other operating expenses and net operating cash flow; the potential of DecisionDx-Melanoma to aid in risk-aligned treatment plans for improved patient outcomes and survival rates; the potential of TissueCypher testing to change clinical practice when incorporated into patient management plans; our expectation that we will achieve net operating cash flow positivity by 2025; our expectation that our focused growth investments will contribute to long-term profitability; our milestone expectations regarding the Palmetto/MolDx draft LCD for DecisionDx-SCC, finalization of a Palmetto/Noridian 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, new GI and MyPath/DiffDx commercial team expansion reaching optimal productivity in Q2 2023, expected closure of our San Diego lab by the end of 2022; 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; 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; 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,” “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 accuracy of our assumptions and expectations underlying our three-year revenue and other financial targets (including, without limitation, our assumptions or expectations regarding: (i) continued reimbursement for our DecisionDx-SCC test at the current rate and reimbursement for our other products and subsequent coverage decisions, (ii) our estimated total addressable markets for our products and product candidates and the related expenses, capital requirements and potential needs for additional financing, (iii) the anticipated cost, timing and success of our product candidates, and our plans to research, develop and commercialize new tests and (iv) our ability to successfully integrate new businesses, assets, products or technologies acquired through previously completed acquisitions), 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 September 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.
## Financial Performance Summary Q3 2022

<table>
<thead>
<tr>
<th></th>
<th>3Q21</th>
<th>3Q22</th>
<th>Nine Months Ended September 30, 2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total test reports</td>
<td>7,727</td>
<td>12,114</td>
<td>31,775</td>
</tr>
<tr>
<td>Total Derm test reports</td>
<td>7,352</td>
<td>9,824</td>
<td>27,363</td>
</tr>
<tr>
<td>Revenue</td>
<td>$23.5M</td>
<td>$37.0M</td>
<td>$98.7M</td>
</tr>
<tr>
<td>Adj. Revenue¹</td>
<td>$23.6M</td>
<td>$37.3M</td>
<td>$100.6M</td>
</tr>
<tr>
<td>Gross Margin</td>
<td>77.9%</td>
<td>69.8%</td>
<td>71.1%</td>
</tr>
<tr>
<td>Adj. Gross Margin¹</td>
<td>80.9%</td>
<td>76.2%</td>
<td>77.6%</td>
</tr>
<tr>
<td>Operating Cash Flow</td>
<td>$(6.1)M</td>
<td>$(5.2)M</td>
<td>$(35.7)M</td>
</tr>
<tr>
<td>Adj. Operating Cash Flow¹</td>
<td>$(3.0)M</td>
<td>$(5.2)M</td>
<td>$(35.7)M</td>
</tr>
<tr>
<td>Cash, Cash Equivalents &amp;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marketable Investment Securities</td>
<td>as of end of period</td>
<td>$363M</td>
<td>$266M²</td>
</tr>
</tbody>
</table>

¹See Non-GAAP reconciliations at the end of this presentation. ²Cash use includes acquisitions of AltheaDx and Cernostics.
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
Castle Is Focused on Improving Health through Innovative Tests That Guide Patient Care

Answering clinical questions to guide care along the patient journey
Three Strategic Guideposts That Create Value for Customers, Patients and Stockholders

Customer & Solution Centric
We value best-in-class customer experience at all points along the testing journey, and we leverage multiple solutions for a single customer to provide a single source of high quality molecular diagnostic tests.

Continuous Evolution & Improvement
We are an industry leader by challenging the status quo with deep scientific expertise, unique value insight, and robust data development.

Exceptional Employees
We hire and keep the right people, by Castle’s commitment to doing the right thing for employees and nurturing our thriving culture.
Driving Long-Term Growth through Strong Execution and our Operational Guideposts

Exceptional Employees, Continuous Evolution & Improvement and Customer & Solution Centric
Answering Clinical Questions to Guide Care along the Patient Journey

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

PATIENT CARE JOURNEY

Screening  Diagnostic Support  Risk Stratification  Therapy Resource  MRD/Recurrence Monitoring

Dermatology

Uveal Melanoma

Gastroenterology

Mental Health

Inflammatory Skin Disease Pipeline Test

Castle Biosciences
## Estimated ~$8B U.S. Total Addressable Market\(^1\) for Commercially Available Tests

<table>
<thead>
<tr>
<th>Dermatology</th>
<th>Gastroenterology</th>
<th>Mental Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous melanoma/risk of metastasis, SLNB positivity risk</td>
<td>Cutaneous squamous cell carcinoma/risk of metastasis</td>
<td>Barrett’s esophagus/risk of progression to esophageal cancer</td>
</tr>
<tr>
<td>~130K Patients classified as Stage I, II or III(^2)</td>
<td>~200K Patients w/high-risk features(^2)</td>
<td>~415K Patients receiving upper GI endoscopies/year who meet the intended use criteria for TissueCypher(^3)</td>
</tr>
<tr>
<td>~$540M</td>
<td>~$820M</td>
<td>~$1B</td>
</tr>
<tr>
<td>Suspicious pigmented lesions/melanoma status</td>
<td>~300K Patients w/ diagnostically ambiguous lesions</td>
<td>Mental health therapy response</td>
</tr>
<tr>
<td>~$600M</td>
<td></td>
<td>Based on indicated use of IDgenetix for patients diagnosed with depression, anxiety and other mental health conditions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>~$5B</td>
</tr>
</tbody>
</table>

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)

\(^1\)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
Committed to Delivering Long-term Growth with Net Operating Cash Flow Positivity by 2025

<table>
<thead>
<tr>
<th></th>
<th>Three-year plan (2025)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revenue</td>
<td>25-35% year-over-year growth(^1); Total revenue in 2025 of $255m-$330m</td>
</tr>
<tr>
<td>Adjusted Gross Margins</td>
<td>80%-85% by 2025</td>
</tr>
<tr>
<td>Other Operating Expenses(^2)</td>
<td>75%-85% of revenue by 2025</td>
</tr>
<tr>
<td>Net Operating Cash Flow</td>
<td>Positive(^3)</td>
</tr>
</tbody>
</table>

\(^1\)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
Q3 2022 Operating Expenses
Executed planned investments to support our growth initiatives for long-term value creation

Key Drivers for Q3 2022 OpEx

- **Cost of Sales** – Higher personnel costs due to headcount additions, particularly in our laboratories related to recent acquisitions. Higher laboratory activity, which is attributable to higher test volumes, also increased costs of supplies and services.

- **R&D** – Higher personnel costs associated with our increased headcount to manage and run our clinical studies, which include expenses related to salaries, wages and stock-based compensation as well as higher inventory usage to support R&D activities and higher costs for clinical studies.

- **SG&A** – Higher personnel costs associated with headcount expansion in our dermatology, GI and mental health commercial teams, which include expenses related to salaries, stock-based compensation and bonuses.

- **Amortization of Acquired Intangible Assets** – Related to MyPath Melanoma, TissueCypher and IDgenetix tests.

### Operating Expense by Quarter

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Cost of Sales</th>
<th>R&amp;D</th>
<th>SG&amp;A</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q3 2021</td>
<td>$35.3</td>
<td></td>
<td></td>
<td>$38.6</td>
</tr>
<tr>
<td>Q4 2021</td>
<td>$40.2</td>
<td></td>
<td></td>
<td>$38.8</td>
</tr>
<tr>
<td>Q1 2022*</td>
<td>$51.4</td>
<td></td>
<td></td>
<td>$58.6</td>
</tr>
<tr>
<td>Q2 2022</td>
<td>$51.9</td>
<td></td>
<td></td>
<td>$58.2</td>
</tr>
<tr>
<td>Q3 2022</td>
<td>$51.9</td>
<td></td>
<td></td>
<td>$58.2</td>
</tr>
</tbody>
</table>

*Key: Change in fair value of contingent consideration
Intangible Asset Amortization
SG&A
R&D
Cost of sales

*Amounts in millions. Operating expenses rounded and summarized as presented.
Key Q3 and Recent 2022 Accomplishments

- Achieved strong growth over Q3 2021 in total revenue (+58%) and achieved a new record in total test report volume (12,114, +57% compared to Q3 2021)
- Presented three-year financial targets and strategic guideposts at 2022 Investor Day
- AGA Clinical Practice Update released with best practice advice for the potential utilization of TissueCypher to risk stratify patients with non-dysplastic Barrett’s esophagus
- Expanded evidence supporting Dermatology and Uveal Melanoma tests through the publication of four new peer-reviewed studies
- Received AZBio Fast Lane Award from the Arizona Bioindustry Association (AZBio), recognizing Castle’s achievement of outstanding milestones in the last 18 months

1Jarell et al. JAAD 2022 (DecisionDx-Melanoma); Ahmed et al. Cancer Medicine 2022 (DecisionDx-Melanoma); Williams et al. Melanoma Management 2022 (DecisionDx-UM); Hooper et al. Cancer Investigation 2022 (DecisionDx-SCC)
Expected Upcoming Milestones

- Expected publication of collaborative NCI study showing higher melanoma specific survival for patients tested with DecisionDx-Melanoma
- Expected finalization of Palmetto/Noridian 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
- Two-year TissueCypher ADLT rate beginning Jan. 1, 2023
First-to-Market Dermatologic Franchise, Additional Growth Opportunities

Diagnostic Support

Risk Stratification

Therapy Response\(^1\)

Strong provider growth and continued adoption with \(~2,335\) new ordering clinicians and \(~9,155\) unique ordering clinicians for our dermatologic tests over the last 12 months\(^2\)

\(^1\)Target launch anticipated by the end of 2025

\(^2\)New and unique ordering clinicians for all dermatologic tests combined between Oct. 1, 2021-Sept. 30, 2022
Traditional Approaches to Staging Melanoma Miss Patients with Aggressive Tumor Biology

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

**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).

Based on a recent study, patients were found to be **2x as likely to survive** if they had asymptomatic recurrence detected, compared to those who had symptoms at the time their recurrence was detected.

*Excludes stage IV*
DecisionDx-Melanoma Provides Answers for Two Critical Clinical Questions

DecisionDx-Melanoma test results predict a patient’s individual risk of recurrence and individual risk of sentinel lymph node positivity using two proprietary algorithms.

Whitman et al. JCO PO 2021; Jarell et al. JAAD 2022
### DecisionDx-Melanoma GEP Has Consistent and Independent Evidence of Prognostic Value across Studies

#### FEATURE

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

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

- **Class 1A Lowest Risk**
  - Quantifies expression of 31 genes from primary tumor using RT-PCR
  - Applies validated algorithm

- **Class 1B/2A Increased Risk**

- **Class 2B Highest Risk**
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

<table>
<thead>
<tr>
<th></th>
<th>3-year OS (95% CI)</th>
<th>Deaths, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31-GEP Tested</td>
<td>93.1% (92.0-94.2%)</td>
<td>4.8% (174/3,621)</td>
</tr>
<tr>
<td>Matched Untested</td>
<td>91.2% (90.4-91.9%)</td>
<td>6.1% (658/10,863)</td>
</tr>
<tr>
<td>Hazard Ratio^4</td>
<td>0.79 (0.67-0.93)</td>
<td>P=0.006</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>3-year MSS (95% CI)</th>
<th>Deaths, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31-GEP Tested</td>
<td>97.7% (97-98.4%)</td>
<td>1.6% (58/3,621)</td>
</tr>
<tr>
<td>Matched Untested</td>
<td>96.6% (96.2-97.1%)</td>
<td>2.2% (238/10,863)</td>
</tr>
<tr>
<td>Hazard Ratio^4</td>
<td>0.73 (0.54-0.97)</td>
<td>P=0.03</td>
</tr>
</tbody>
</table>

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.

^4 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.

Kurley et al. Presented at European Association of Dermato Oncology (EADO) conference in Seville, Spain; April 21-23, 2022
**DecisionDx-Melanoma Disease Specific Survival Outcomes are Favorable Relative to Other Tests**

**Sentinel lymph node biopsy (SLNB)**
- SLNB is a risk-stratification surgical procedure “test” in melanoma
- MSLT-1 found that SLNB had no impact on 10-year melanoma-specific survival

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>P-value</th>
<th>10-yr MSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin (&lt;1.2mm)</td>
<td>Not reported</td>
<td>Not impacted</td>
</tr>
<tr>
<td>Intermediate (1.2-3.5mm)</td>
<td>not significant (p=.18)</td>
<td>Not impacted</td>
</tr>
<tr>
<td>Thick (&gt;3.5)</td>
<td>not significant (p=.56)</td>
<td>Not impacted</td>
</tr>
</tbody>
</table>

**Breast Cancer Test**

<table>
<thead>
<tr>
<th>Test</th>
<th>3-yr BCSS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer Test</td>
<td>99.6%</td>
</tr>
<tr>
<td>Matched Untested</td>
<td>99.1%</td>
</tr>
<tr>
<td>Absolute Mortality Difference</td>
<td><strong>0.50% (p&lt;0.05)</strong></td>
</tr>
</tbody>
</table>

BCSS mortality difference of **0.50% at 3 years** when comparing tested and untested populations

<table>
<thead>
<tr>
<th>Test</th>
<th>3-yr MSS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DecisionDx-Melanoma</td>
<td>97.7%</td>
</tr>
<tr>
<td>Matched Untested</td>
<td>96.6%</td>
</tr>
<tr>
<td>Absolute Mortality Difference</td>
<td><strong>1.1% (p&lt;0.05)</strong></td>
</tr>
</tbody>
</table>

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

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Patients with Melanoma Desire Testing with DecisionDx-Melanoma

Data from a patient study conducted in collaboration with the Melanoma Research Foundation

- **90%** wanted prognostic information about their melanoma tumors at diagnosis.
- **92%** felt the testing was useful.
- **77%** wanted testing to obtain all of the information they could about their melanoma.
- **54%** of the patients who did not receive 31-GEP testing 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.
DecisionDx-Melanoma Is Supported by Significant Scientific Evidence

<table>
<thead>
<tr>
<th>9,000+</th>
<th>36+</th>
<th>112,820+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients included in studies including <em>independent validation</em></td>
<td>Peer-reviewed, published studies including <em>prospective studies</em> and 2 meta-analyses</td>
<td>Patients with a clinical DecisionDx-Melanoma order from 10,750+ clinicians</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1A</th>
<th>50%</th>
<th>Medicare+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1A evidence*</td>
<td><em>Demonstrated change</em> in management for 1 of 2 patients tested</td>
<td>Covered by Medicare and multiple private insurers with an <em>industry-leading</em> patient assistance program</td>
</tr>
</tbody>
</table>

*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. Data as of Sept. 30, 2022.*
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.
How is Risk Assessment Traditionally Done for SCC Patients?

- The SCC community uses the term “high-risk” SCC to describe different patient populations.

- Current SCC staging fails to identify >30% of cases who will go on to experience metastasis.

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)

NCCN

1. HR
2. or
Mohs AUC

>2 cm,
Deep
(broad definition),
PNI
(broad def'),
Poorly
differentiated,
LVI,
Ear, Lip, Temple
Scalp
Immunocompromised

BWH

1. T2a
2. Any 1 of:
3. >2 cm,
4. Deep (>SC fat),
5. LVI,
6. PNI (≥0.1mm),
7. Poorly diff'

BWH

1. T2b
2. Any 2-3 of:
3. >2 cm,
4. Deep (>SC fat),
5. PNI (≥0.1mm),
6. Poorly diff'

Broader Criteria

“HIGH RISK”

Narrower Criteria

Higher PPV

1 NCCN Guidelines for Squamous Cell Skin Cancer v2.2022;
2 Connolly et al. J AAD 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
DecisionDx-SCC Predicts Metastatic Risk For SCC Patients With One Or More Risk Factors

**DecisionDx-SCC**

- Quantifies expression of 40 genes from primary tumor using RT-PCR
- Applies a validated neural network algorithm
- Accurately classifies patients as low, moderate or high biological risk

**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

SCC patients with one or more risk factors

Wysong et al. JAAD 2021; Ibrahim et al. Future Oncology 2021
Decisiondx-scc Is Validated To Predict Metastatic Risk For Individual SCC Patients With One Or More Risk Factors

![Kaplan-Meier Estimated MFS](image)

Class 1 - Low Biological Risk
- <7% risk of metastasis;
- Less than half the general study population risk

Class 2A - Moderate Biological Risk
- 20% risk of metastasis;
- Similar to the strongest traditional factors

Class 2B - High Biological Risk
- ≥50% risk of metastasis

Cohort Distribution:
- Class 1
- Class 2A
- Class 2B

Wysong et al. JAAD 2021; Ibrahim et al. Future Oncology 2021
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.
Diagnostic GEP is Designed to Provide Clinically Actionable, Objective Results for Nearly All Patients

By leveraging our second GEP test, >98% of patients with ambiguous melanocytic lesions received a clinically actionable result.1,2

1Goldberg et al. SKIN 2021: s792; 2Both tests can be ordered independently. Unless DiffDx-Melanoma is specifically requested, we run MyPath first. If the case results in an intermediate result or fails to produce a result, DiffDx-Melanoma will be run second to provide additional diagnostic clarity.
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

- **85%** of low-grade patients are downgraded upon expert GI pathology review

- **25%** of high-grade/cancer diagnoses occur within 1 year of endoscopy

---

**Pathology (% progression/year)**

- **NDBE** (0.63%)
- **IND** (1.5%)
- **LGD** (1.7%)
- **HGD** (10%)

---

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

Molecular biomarkers to detect changes in the context of tissue structure prior to morphologic changes.

Vision systems that objectively and reproducibly analyze and interpret tissue structures and features.

Peer-reviewed publications that demonstrate the effectiveness of the test.

A risk classifier trained on a large data set to recognize progressor vs non-progressor tissue samples.
The World’s First Prognostic AI-driven Precision Medicine Test for Barrett’s Esophagus

Individualize 5-year risk of progression to HGD or EAC

- Indicated for NDBE, IND, and LGD

- High Risk score enables increased surveillance or early intervention to prevent cancer

- Low Risk score minimizes over treatment and supports extension of surveillance intervals to guideline recommendations
TissueCypher Is the Strongest Independent Predictor of Progression

Original Pathologic Diagnosis

- LGD (n=243)
- IND (n=63)
- ND (n=392)

TissueCypher

- High risk (n=112)
- Inter risk (n=96)
- Low risk (n=491)

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

Consideration of Patient Management Based on Risk of Progression

Endoscopic Eradication Therapy (EET) or 6–12-month surveillance

1-year surveillance

3–5-year surveillance

Histology only  Low-Risk TissueCypher  High-Risk TissueCypher

How Incorporation of TissueCypher Testing Can Change Clinical Practice

Clinical guideline based on histology and segment length

<table>
<thead>
<tr>
<th>NDBE</th>
<th>IND</th>
<th>LGD</th>
</tr>
</thead>
</table>
| Surveillance in 3 to 5 years\(^1,2,3\)  
3 years if segment length \(\geq 3\) cm
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

<table>
<thead>
<tr>
<th>NDBE</th>
<th>IND/LGD BE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider surveillance in 3 to 5 years</td>
<td>Consider surveillance in 12 months and PPIs as needed</td>
</tr>
</tbody>
</table>

LOW Risk Class

HIGH/INT Risk Class

<table>
<thead>
<tr>
<th>NDBE</th>
<th>IND/LGD BE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rule out prevalent HGD/EAC and consider EET or surveillance in 1 year</td>
<td>Rule out prevalent HGD/EAC and consider EET and PPIs as needed</td>
</tr>
</tbody>
</table>

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
Medication Selection for Mental Illness Is Challenging

<table>
<thead>
<tr>
<th>Inadequate Therapy Response</th>
<th>Low Remission Rates</th>
<th>High Prevalence of Adverse Drug Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>~53% of patients with major depressive disorder (MDD) have an inadequate response to first-line treatment&lt;sup&gt;1&lt;/sup&gt;</td>
<td>72% of patients with MDD do not achieve remission using current standard of care treatment approaches&lt;sup&gt;2&lt;/sup&gt;</td>
<td>The likelihood of discontinuation rises from 8.6% with first-line medication treatment to 41.4% with fourth-line treatment&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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

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

Response Rate
≥ 50% Reduction from Baseline

<table>
<thead>
<tr>
<th></th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>28%</td>
<td>9%</td>
</tr>
<tr>
<td>IDgenetix</td>
<td>55%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Remission Rate
Patients Achieving Remission

<table>
<thead>
<tr>
<th></th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>IDgenetix</td>
<td>25%</td>
<td>35%</td>
</tr>
</tbody>
</table>

>2.5x increase in remission rate vs. control

2x increase in response rate vs. control

# Precision Medicine Designed to Streamline Medication Selection for Mental Health

IDgenetix is redefining the standards of next generation PGx

<table>
<thead>
<tr>
<th>Feature</th>
<th>IDgenetix</th>
<th>PGx Original</th>
<th>Trial &amp; Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-Gene Test</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>RCT/Clinical Utility</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Medicare Coverage</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Comorbidity (MDD &amp; Anxiety)</td>
<td>✔️</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-Drug Interactions</td>
<td>✔️</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifestyle Factors</td>
<td>✔️</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DecisionDx-UM: the Standard of Care in the Management of Newly Diagnosed Uveal Melanoma

Strong Evidence Base

• 24 peer-reviewed publications, **3,100+ patients**

Widespread Adoption

• Nearly **8 in 10 patients** diagnosed with uveal melanoma in the U.S. receive the DecisionDx-UM test as part of their diagnostic workup
• **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
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 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, the most directly comparable GAAP measure, for 2025 because we are unable to predict certain items contained in the GAAP measure without unreasonable efforts.
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 previous slide for further information regarding the Company’s use of non-GAAP financial measures.

<table>
<thead>
<tr>
<th>(in thousands)</th>
<th>Three Months Ended September 30</th>
<th>Nine Months Ended September 30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2022</td>
<td>2021</td>
</tr>
<tr>
<td><strong>Adjusted revenue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net revenues (GAAP)</td>
<td>$37,011</td>
<td>$23,475</td>
</tr>
<tr>
<td>Revenue associated with test reports delivered in prior periods</td>
<td>277</td>
<td>92</td>
</tr>
<tr>
<td><strong>Adjusted revenue (Non-GAAP)</strong></td>
<td>$37,288</td>
<td>$23,567</td>
</tr>
<tr>
<td><strong>Adjusted gross margin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross margin (GAAP)</td>
<td>$25,846</td>
<td>$18,281</td>
</tr>
<tr>
<td>Amortization of acquired intangible assets</td>
<td>2,306</td>
<td>694</td>
</tr>
<tr>
<td>Revenue associated with test reports delivered in prior periods</td>
<td>277</td>
<td>92</td>
</tr>
<tr>
<td><strong>Adjusted gross margin (Non-GAAP)</strong></td>
<td>$28,429</td>
<td>$19,067</td>
</tr>
<tr>
<td>Gross margin percentage (GAAP)</td>
<td>69.8 %</td>
<td>77.9 %</td>
</tr>
<tr>
<td>Adjusted gross margin percentage (Non-GAAP)</td>
<td>76.2 %</td>
<td>80.9 %</td>
</tr>
</tbody>
</table>

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).
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 47 for further information regarding the Company’s use of non-GAAP financial measures.

<table>
<thead>
<tr>
<th>(in thousands)</th>
<th>Three Months Ended September 30,</th>
<th>Nine Months Ended September 30,</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2022</td>
<td>2021</td>
</tr>
<tr>
<td>Net cash used in operating activities (GAAP)</td>
<td>$ (5,224)</td>
<td>$ (6,133)</td>
</tr>
<tr>
<td>Medicare advance payment¹</td>
<td>—</td>
<td>3,178</td>
</tr>
<tr>
<td>HHS provider relief funds²</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Adjusted operating cash flow (Non-GAAP)</td>
<td>$ (5,224)</td>
<td>$ (2,955)</td>
</tr>
</tbody>
</table>

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).
Appendix
ESG Focus Areas for 2022 and Beyond

- Environmental policy
- Environmental metrics
- DEI statement
- DEI metrics
- DEI action plan/roadmap
- Vendor code of conduct/supplier standard

In 2022, Castle Biosciences received a rating of AA (on a scale of AAA-CCC) in the MSCI ESG Ratings assessment.
Employee Engagement is Part of our Core Strategy for Success

Based on the results of Castle’s annual employee survey

### 2022
- **Castle employee engagement score:** 81%
- **Healthcare benchmark average engagement score:** 53%
- **Response Rate:** 89%
- **Healthcare benchmark response rate:** 59%

### 2021
- **Castle employee engagement score:** 83%
- **Healthcare benchmark average engagement score:** 66%
- **Response Rate:** 86%
- **Healthcare benchmark response rate:** 63%

1 Data from June 2022 employee engagement survey administered by Energage
Commitment to Diversity

**ETHNICITY/RACE**

- **ALL EMPLOYEES**
  - 73.6%
  - AMERICAN INDIAN OR ALASKA NATIVE: 1.0%
  - ASIAN: 3.9%
  - BLACK OR AFRICAN AMERICAN: 7.1%
  - HISPANIC: 11.2%
  - NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER: 0.2%
  - TWO OR MORE RACES (NOT HISPANIC OR LATINO): 3.0%
  - WHITE: 87.1%

- **EXECUTIVES**
  - 35.5%
  - AMERICAN INDIAN OR ALASKA NATIVE: 3.2%
  - ASIAN: 6.5%
  - BLACK OR AFRICAN AMERICAN: 3.2%
  - HISPANIC: 3.2%
  - NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER: 6.5%
  - TWO OR MORE RACES (NOT HISPANIC OR LATINO): 3.2%
  - WHITE: 87.1%

**GENDER**

- **TOTAL EMPLOYEES = 492**
  - 65.7%
    - FEMALE: 34.3%
    - MALE: 65.7%

- **EXECUTIVES**
  - 64.5%
    - FEMALE: 35.5%
    - MALE: 64.5%

Data as of 8/1/22; Executive= Executive Director or Regional Business Director level and above
Award-Winning Company

Committed to cultivating a culture of innovation, continuous growth and advancement
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**
- **Mara Aspinall**
- **Brad Cole**
- **Tiffany Olson**
- **Miles D. Harrison**
- **Kimberlee Caple**
- **Ellen Goldberg**

(Credentials and affiliations listed for each individual)