



Transforming Disease
Management

May 9, 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: estimated sizes of the total addressable markets of our current and future commercial and pipeline products within our dermatologic, GI and mental health franchises; our revised revenue outlook for the 2022 fiscal year, including 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 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; 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; 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,” “estimates,” “expects,” “intends,” “may,” “plans,” “will” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions, or expectations disclosed in our forward-looking statements and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements that we make. These forward-looking statements involve risks and uncertainties that could cause our actual results to differ materially from those in the forward-looking statements, including, without limitation, the effects of the COVID-19 pandemic on our business and our efforts to address its impact on our business, subsequent study results and findings may contradict earlier study results and findings, 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 March 31, 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.

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 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



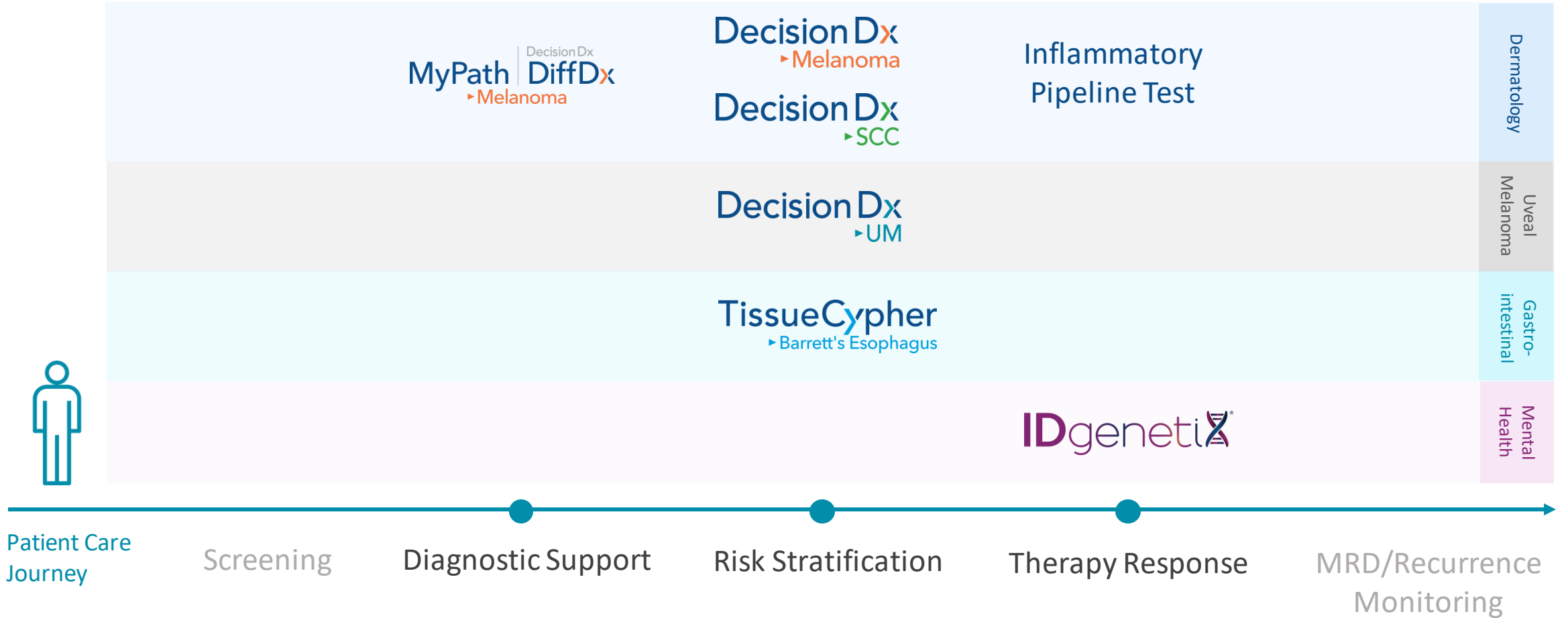
Provide robust data to support the clinical value of our tests



Accelerate test adoption through commercial excellence

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





Financial Performance Summary Q1 2022

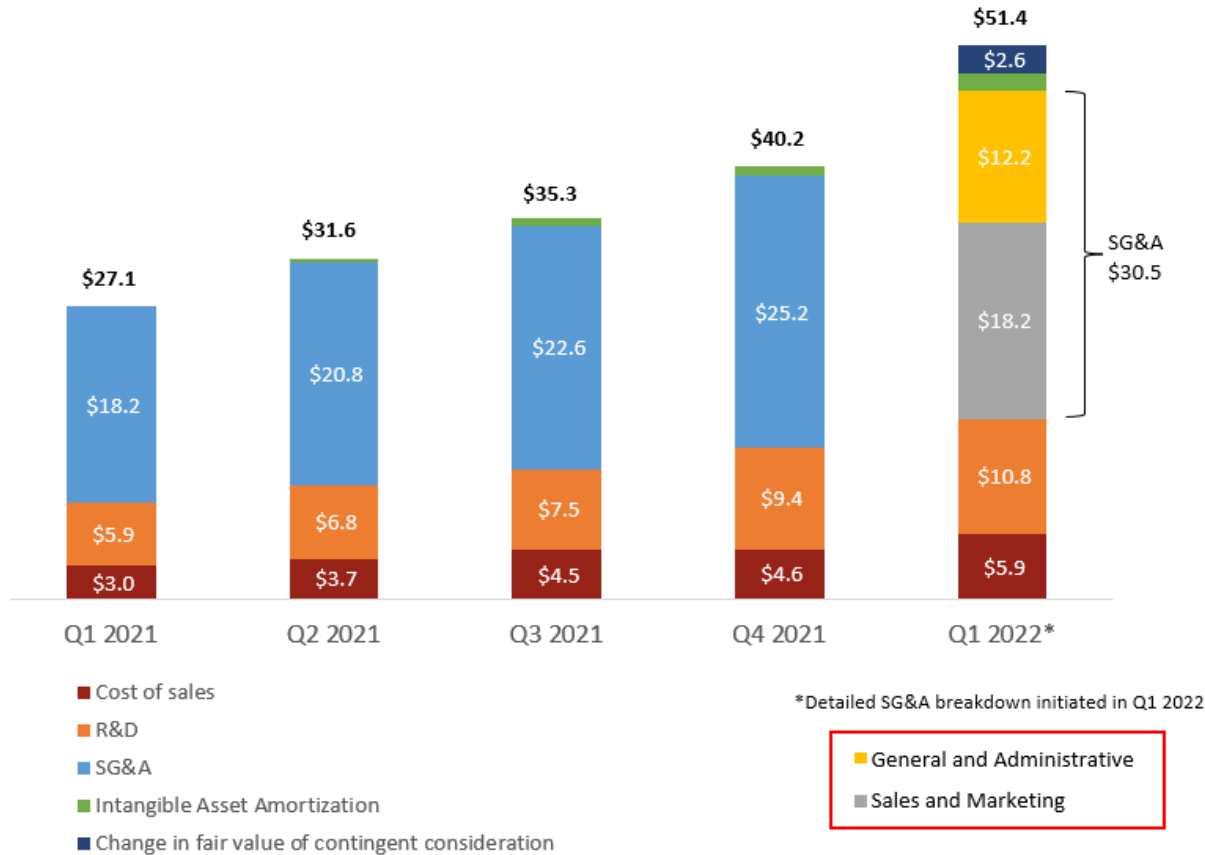
	1Q22	1Q21
Revenue	\$26.9M	\$22.8M
Adj. Revenue ¹	\$26.3M	\$17.5M
Total test reports	8,627	5,142
Total Derm test reports	8,115	4,805
Operating Cash Flow	\$(21.4)M	\$(3.6)M
Adj. Operating Cash Flow ¹	\$(21.4)M	\$(5.5)M
Gross Margin	71.7%	86.7%
Adj. Gross Margin ¹	77.4%	82.7%
Cash & Cash Equivalents	\$309M as of 03/31/2022	\$407M as of 03/31/2021



Q1 2022 Operating Expenses

Increased investments to support our growth initiatives for long-term value creation

Operating Expense by Quarter¹



Key drivers for Q1 2022 OpEx

Cost of Sales - Scaling of Pittsburgh lab; preparation for volume ramp for TissueCypher, DecisionDx-SCC and DiffDx-Melanoma ahead of anticipated reimbursement

R&D - Higher personnel costs associated with our increased headcount to manage and run our clinical studies, which include expenses related to salaries, bonuses, benefits and stock-based compensation and increases in other expenses associated with increased clinical study activity

SG&A - Higher personnel costs associated with our increased headcount (including GI commercial team), which include expenses related to salaries, bonuses, benefits and stock-based compensation

Intangible Asset Amor. - related to myPath Melanoma and TissueCypher tests

Contingent Consideration - related to remeasurement of Cernostics earnout payments





Full-Year 2022 Guidance

	As of Feb. 28, 2022 ¹	As of May 9, 2022 ² (all include incremental of AltheaDx acquisition)	Key Drivers
Revenue	\$115 - \$120 million	\$118 - \$123 million	Further consistent execution on our growth plans and in particular the AltheaDx acquisition
Cost of Sales (exclusive of amortization of acquired intangible assets)	65%-75% growth	75%-85%	Scaling of Pittsburgh lab; preparation for volume ramp for TissueCypher, DecisionDx-SCC and DiffDx-Melanoma ahead of anticipated reimbursement, market adjustments for compensation
R&D Expense	50%-60% growth	55%-65%	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	40%-50%	Addition of gastroenterology team and continued build in dermatology, market adjustments for compensation, accelerated G&A staff expansions to support growth
Stock Based Comp	\$35-40 million	\$40-45 million	Primarily due to increase in headcount to support growth, with pace of additional employees increasing in recent years and 2022

¹Guidance given on February 28, 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.

²Percentage increases compared to the year ended 12/31/21; Cost of sales, R&D and SG&A expense growth includes stock-based comp.

Q1 and Recent 2022 Key Accomplishments



Achieved strong, consistent growth over Q1 2021, in our revenue (+18%), adjusted revenue (+50%) and total test report volume (+68%)



Expanded SEER Registries data shared at the 18th European Association of Dermato Oncology Congress showing patients diagnosed with melanoma and tested with DecisionDx-Melanoma had 27% improvement in melanoma specific survival compared to untested patients



July 1, 2021, dermatology commercial expansion supported report growth of DecisionDx-Melanoma, DecisionDx-SCC and CDO (myPath and DiffDx) of 48%, 117% and 336%, respectively.



Centers for Medicare & Medicaid Services (CMS) granted Advanced Diagnostic Laboratory Test (ADLT) status for TissueCypher, exempting TissueCypher from the 14-Day Rule



Acquisition of AltheaDx and IDgenetix test, with recently expanded Medicare coverage to include seven additional mental health conditions beyond major depressive disorder



U.S. Federal Supply Schedule contract with the VA expanded beyond DecisionDx-Melanoma to include all skin cancer tests

Including IDgenetix, Anticipate an Estimated ~\$8B for Commercially Available U.S. Total Addressable Market¹

Dermatology			Gastroenterology	Mental Health
Cutaneous melanoma/ risk of metastasis	Cutaneous squamous cell carcinoma/ risk of metastasis	Suspicious pigmented lesions/melanoma status	Barrett's esophagus/ risk of progression to esophageal cancer	Mental health therapy response
~130K Patients classified as Stage I, II or III ²	~200K Patients w/ high-risk features ²	~300K Patients w/ indeterminant biopsy ²	~384K Patients receiving upper GI endoscopies/year who meet the intended use criteria for TissueCypher ³	Based on indicated use of IDgenetix for patients diagnosed with depression, anxiety and other mental health conditions
~\$540M	~\$820M	~\$600M	~\$1B	~\$5B

Tests in pipeline add an additional estimated ~\$3.6B to our U.S. TAM
 (\$1.9B for inflammatory pipeline test and ~1.7B for additional dermatology pipeline tests)

10 ¹U.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.
³384,000 upper GI endoscopies/year with confirmed dx of BE (ND, IND, LGD) x \$2,513 = U.S. only TAM of ~\$1 billion



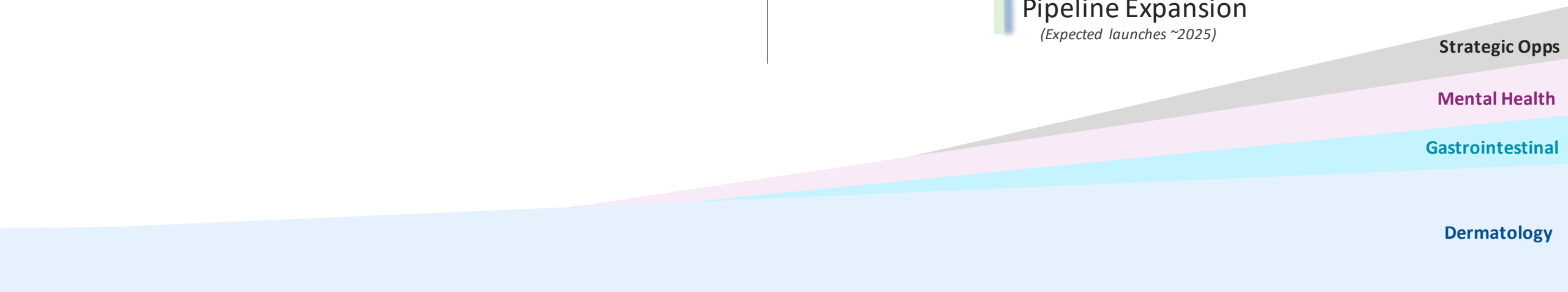
Driving Long-Term Growth through our Foundational Strategy: Strong Core Derm Business, Pipeline Initiatives and Strategic Opportunities

Near-to Mid-term Growth
2022-2023

- Dermatology
- Gastrointestinal
- Mental Health
- Strategic Opportunities

Mid-to Long-term Growth
2024 and beyond

- Dermatology
- Gastrointestinal
- Mental Health
- Strategic Opportunities
- Pipeline Expansion
(Expected launches ~2025)



Operational Growth Pillars

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



- 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



Accelerating Investments in Clinical Development

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

Decision Dx
► Melanoma

Decision Dx-SCC

MyPath | **Decision Dx**
Diff Dx
► Melanoma

Decision Dx
► UM

TissueCypher
► Barrett's Esophagus

4
Ongoing studies

117
Committed sites

~1,700
Patients enrolled

5
Ongoing studies

127
Committed sites

~3,350
Patients enrolled

3
Ongoing studies

25
Committed sites

~3,250
Patients enrolled

1
Ongoing study

3
Committed sites

~30
Patients enrolled

3
Ongoing studies

12
Committed sites

~690
Subjects¹ enrolled

Upcoming Q2-Q3 Data Presentations

SID Annual Meeting
Fall Clinical NP/PA
SDPA
ASCO 2022

ACMS
Fall Clinical NP/PA
SDPA

ISDP
SDPA
SBS 2022

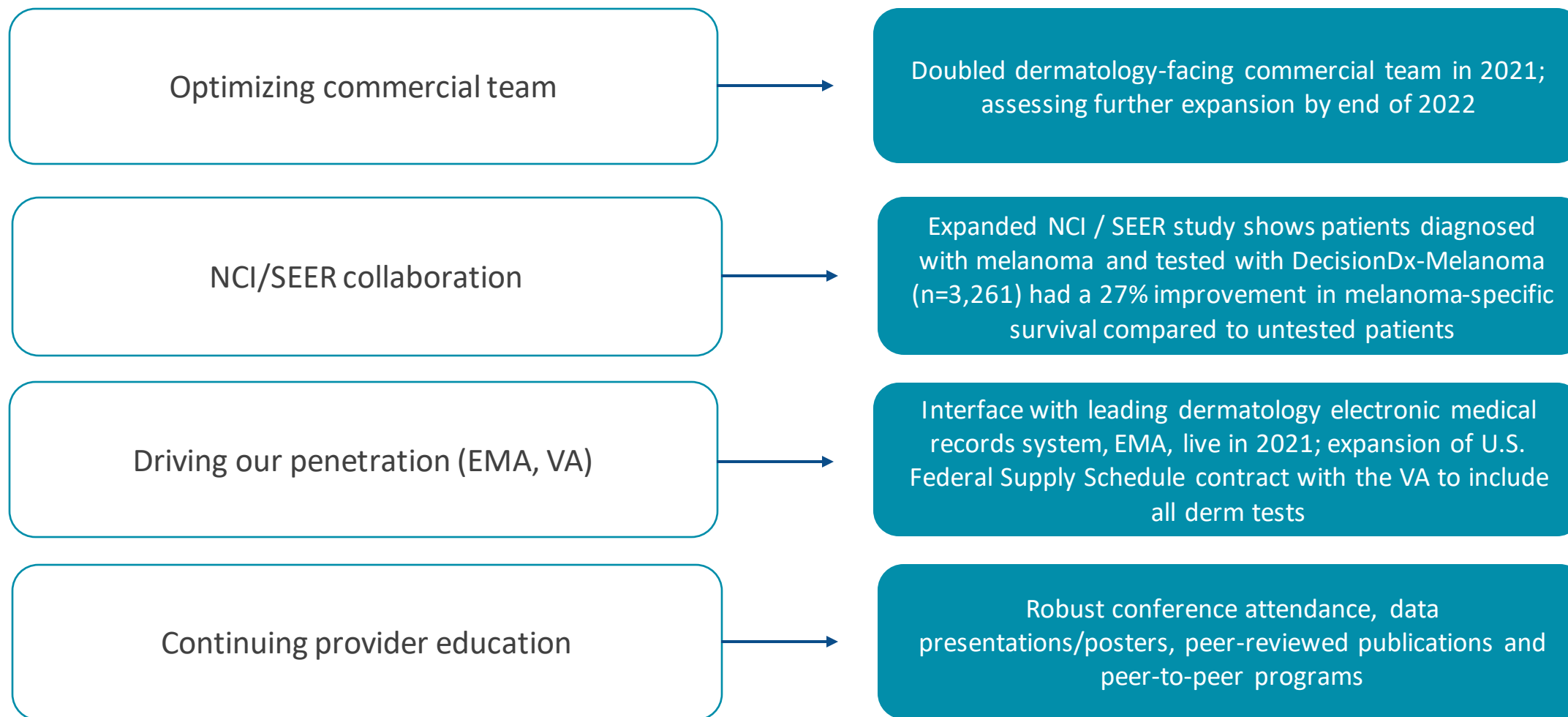
ISOO 2022

DDW 2022

Dermatology

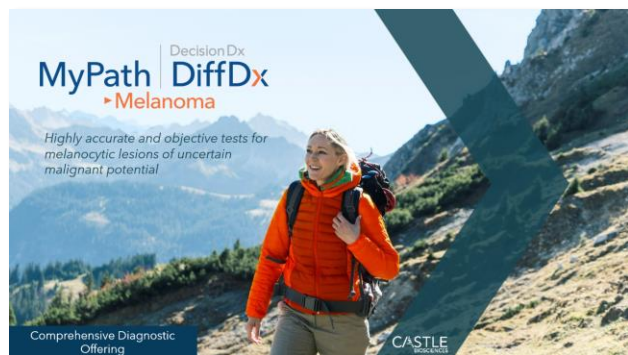


Strong Core Derm Business Pillar of Growth

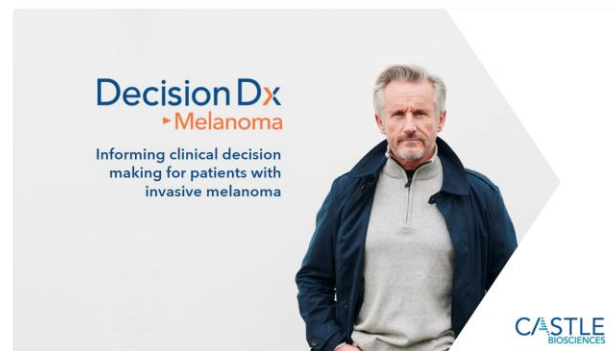


First-to-Market Dermatologic Franchise, Additional Growth Opportunities

Diagnostic Support



Risk-Stratification



Therapy Response¹



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

Market Snapshot	Clinical Questions <i>(post-melanoma diagnosis)</i>	Clinical Utility	Transforming Disease Management
<p>~\$540M revenue opportunity¹</p> <p>~130k patients classified as Stage I, II or III²</p>	<p>Is the risk of SLN-positivity high enough to warrant referral for the SLNB surgery?</p>	<p>Accurately identifies those at low and high risk for a positive SLN³</p>	<p>DecisionDx-Melanoma could result in 74% fewer SLNB surgeries⁷, potentially saving the U.S. healthcare system \$250M^{4,5}</p> <p>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-Stage³</p>
	<p>What is the individual risk of recurrence?</p>	<p>Provides personalized risk of recurrence to give guidance for patient follow-up and treatment intensity decisions</p>	<p>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 results⁶</p>

SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy. Source: NCCN Guidelines for Cutaneous Melanoma v3.2020¹ 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.

³Whitman et al. *JCO Precision Oncology* 2021 ⁴Vetto et al. *Future Oncol* 2019. ⁵Clearview health economic model, data on file

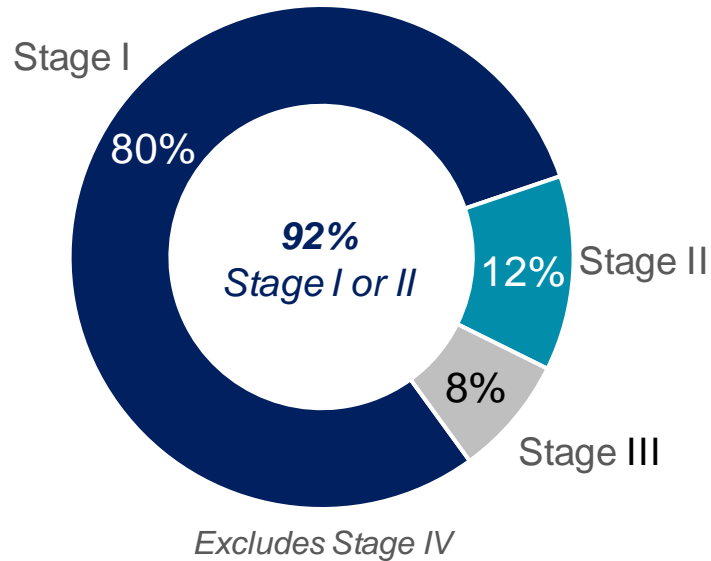
⁶Four consecutive clinical impact studies showed 47-53% change in risk-of-recurrence-based management based on results of testing with DecisionDx-Melanoma: Berger, et al. 2016 *Curr Med Res Opin*; Dillon et al. 2018 *Skin*; Farberg et al. 2017 *Jrnl Drugs Derm*; Schuitevoerder, et al. 2018 *Jrnl Drugs Derm*.

⁷ For patients with melanomas of less than or equal to 2.0 mm thick

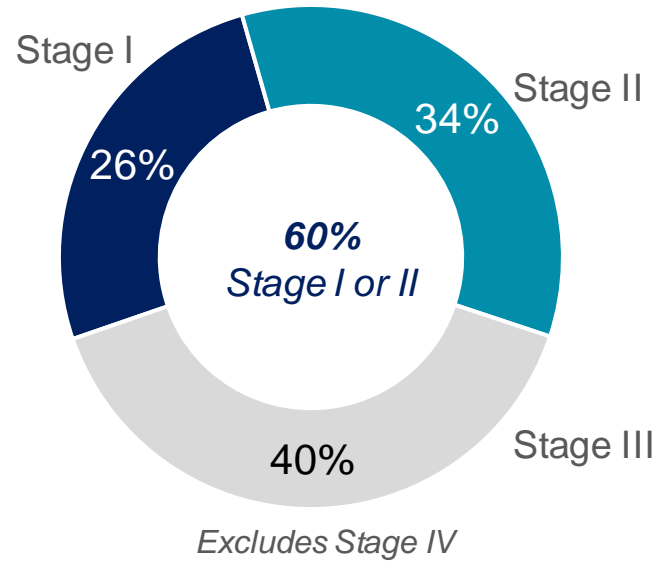


Current Melanoma Staging Misses Patients with Aggressive Tumor Biology

Stage at Diagnosis



Melanoma Deaths by Stage at Diagnosis



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



DecisionDx-Melanoma Is Supported by Significant Scientific Evidence

6,300+

Patients included in studies including *independent validation*

35+

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

97,200+

Patients with a *DecisionDx-Melanoma* order from *9,660 clinicians*

1A

Level 1A evidence*

50%

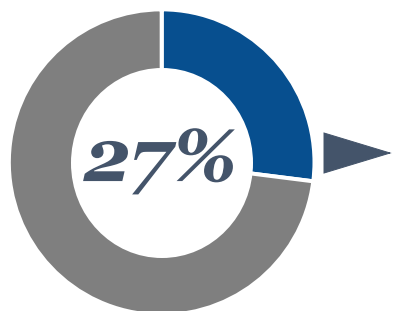
Demonstrated change in management for 1 of 2 patients tested

Medicare+

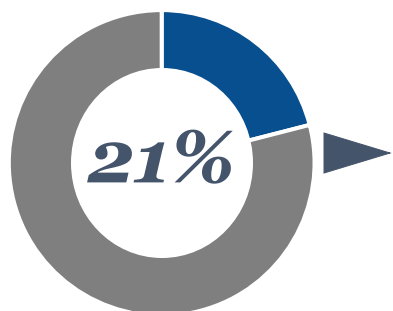
Covered by Medicare and multiple private insurers with an *industry-leading* patient assistance program

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 MSS in patients that were tested at 3 years over those that were not tested



Benefit in OS in patients that were tested at 3 years over those that were not tested

	3-year MSS (95% CI)	Deaths, % (n/N)
31-GEP Tested	97.7% (97.0-98.4%)	1.6% (58/3621)
Matched Untested	96.6% (96.2-97.1%)	2.2% (238/10863)
Hazard ratio[‡]	0.73 (0.54-0.97)	P=0.03

	3-year OS (95% CI)	Deaths, % (n/N)
31-GEP Tested	93.1% (92.0-94.2%)	4.8% (174/3621)
Matched Untested	91.2% (90.4-91.9%)	6.1% (658/10863)
Hazard ratio[‡]	0.79 (0.67-0.93)	P=0.006

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

 DecisionDx-SCC: Predicts Metastatic Risk for SCC Patients with One or More Risk Factors

Market Snapshot	Clinical Question <i>(post-SCC diagnosis)</i>	Clinical Utility	Transforming Disease Management
<p>~\$820M revenue opportunity¹</p> <p>~200k patients with high-risk features²</p>	<p>Who is really at low risk or high risk for metastasis?</p>	<p>Predicts metastatic risk for individual SCC patients with one or more risk factors</p>	<p>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</p>
		<p>Incorporation of DecisionDx-SCC can improve management decisions within established guidelines</p>	<p>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</p>
		<p>Proven significant and independent prognostic value for stratifying risk of metastasis in high-risk SCC patients</p>	<p>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</p>

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

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

²Annual 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)

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

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

10 peer-reviewed publications to date

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

~3,350 patients are currently enrolled in studies from **127 centers**¹

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

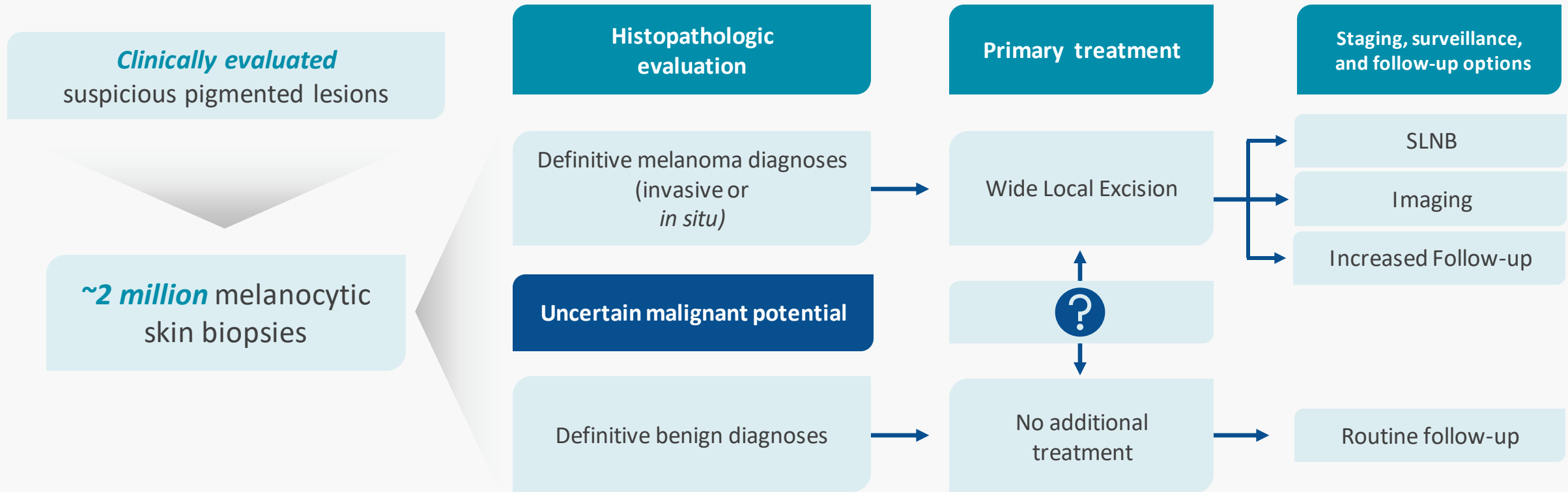
Market Snapshot	Clinical Question	Clinical Utility	Transforming Disease Management
<p>~\$600M revenue opportunity¹</p> <p>~300k patients with an indeterminate biopsy²</p> <p><i>After melanoma diagnosis, clinicians can order DecisionDx-Melanoma using the same tissue sample</i></p>	<p>Is the melanocytic lesion malignant or benign?</p>	<p>Leverages the strengths of myPath Melanoma and DecisionDx DiffDx-Melanoma for the benefit of patient care</p>	<p>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}</p>
		<p>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</p>	<p>Proven utility in reducing ambiguous diagnoses by dermatopathologists and reducing surgical re-excisions by dermatologists in patients with benign GEP results^{5,6,7}</p>
		<p>Adds diagnostic clarity and confidence for more informed patient care</p>	<p>Improves clinically actionable reporting for ~99% of concerning lesions⁷</p>

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

²Annual U.S. incidence for suspicious pigmented lesion biopsies estimated at 2,000,000 with addressable market limited to the 15% with an indeterminate biopsy

³Shoo et al. *J Am Acad Dermatol* 2010; ⁴Lott et al. *JAMA Derm* 2018; ⁵Cokerell et al. *Per Med* 2017; ⁶Cockerell et al. *Medicine* 2016; ⁷Farberg et al. *SKIN J Cutaneous Med* 2020; ⁸Goldberg et al. *SKIN* 2021: s79;

Diagnosing Melanoma, the Clinical Issue: Uncertainty Creates an Over- or Under-Treatment Dilemma

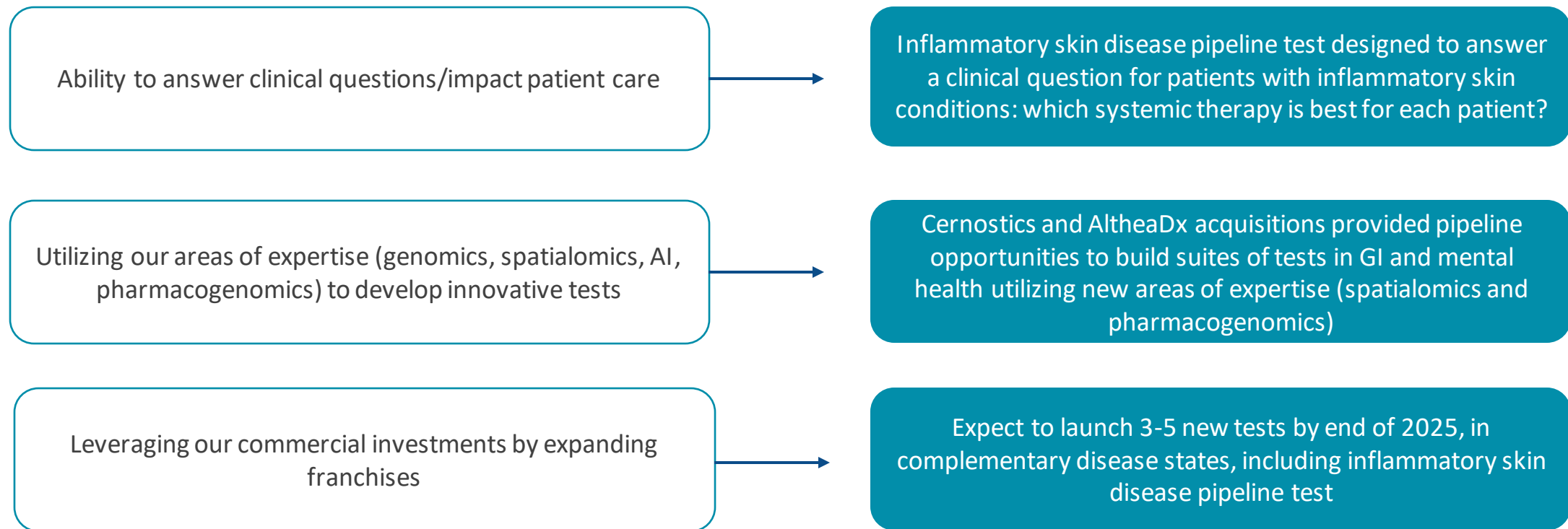




Pipeline Initiatives



Continued Execution on Pipeline Initiatives as a Pillar of Growth



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

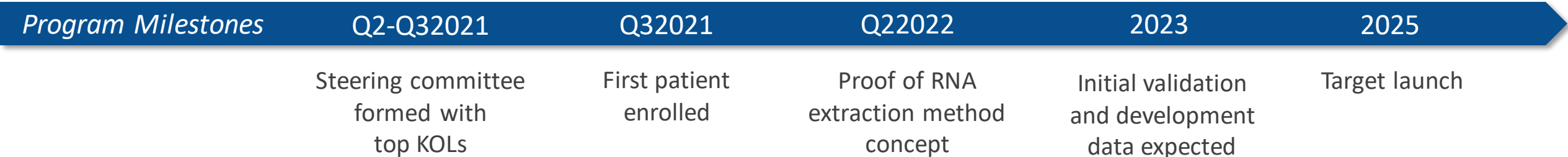
Treatments are significantly different for PSO and AD and can be costly
(e.g., Humira for PSO ~\$68k/year; Dupixent for AD is ~\$38k/year)

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



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

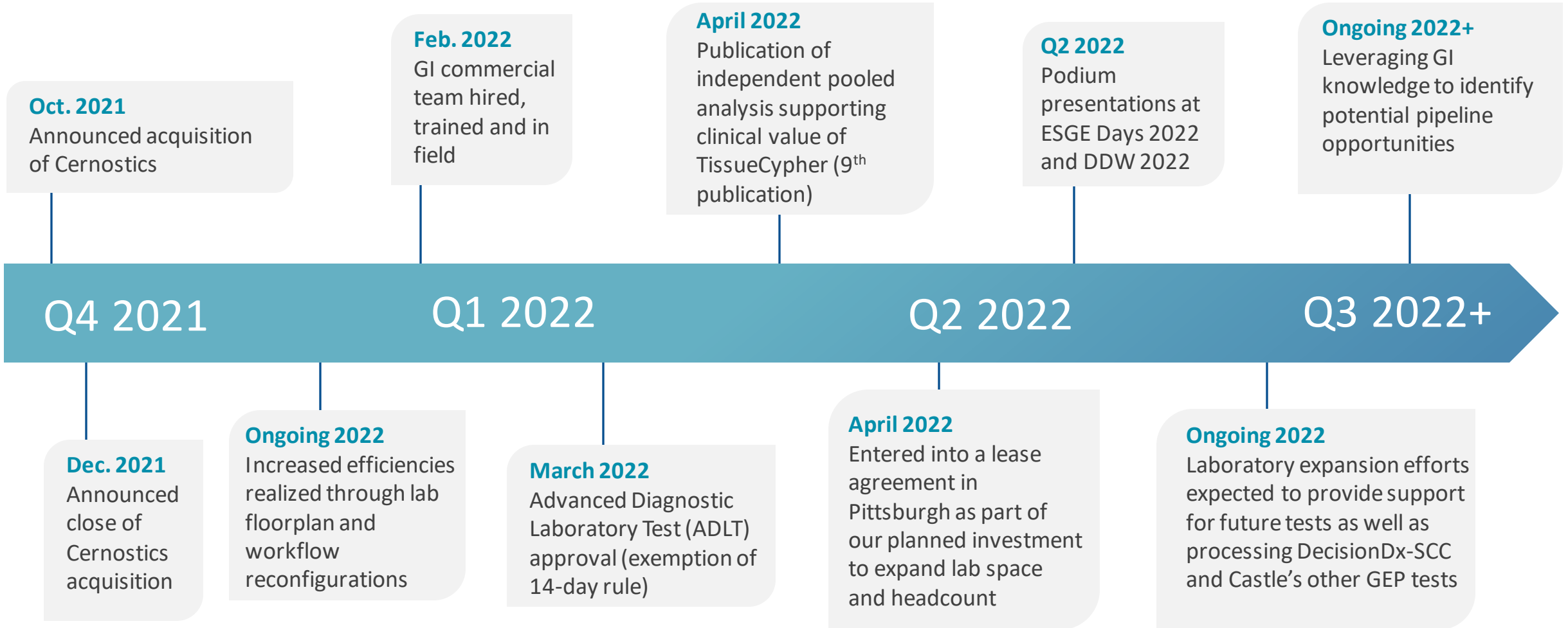


Gastrointestinal



GI/TissueCypher Integration Progress Roadmap: Pittsburgh

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



TissueCypher: Designed to Predict Future Development of Esophageal Cancer in Patients with Barrett's Esophagus (BE)

Market Snapshot	Clinical Decision Point	Clinical Utility	Transforming Disease Management
<p>~\$1B revenue opportunity¹</p> <p>~384k patients receiving upper GI endoscopies/year w/ confirmed Dx of BE²</p>	<p>Which BE patients will progress to HGD or esophageal cancer?</p>	<p>Provides a 5-year individual risk of progression to high-grade dysplasia or esophageal adenocarcinoma for patients with confirmed BE</p>	<p>TissueCypher high risk score independently predicted an almost 8-fold increased risk of progression to esophageal cancer³</p>
		<p>Identifies patients:</p> <ol style="list-style-type: none"> 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 	<p>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 analysis⁴⁻⁸</p> <p>Clinical use study demonstrates 55% change in patient management⁹</p>

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

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

²384,000 upper GI endoscopies/year with confirmed dx of BE (ND, IND, LGD) x \$2,513 = U.S. only TAM of ~\$1 billion

³Iyer, 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)

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

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

Uveal Melanoma



DecisionDx-UM: the Standard of Care in the Management of Newly Diagnosed Uveal Melanoma

Strong Evidence Base

- 22 peer-reviewed publications, **3,100+ 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



C/STLE
BIOSCIENCES

Mental Health

AltheaDx Acquisition Diversifies Castle's Portfolio of Tests and Provides Opportunity for Long-Term Growth Potential

Opportunity

- IDgenetix test represents an estimated ~\$5B U.S. Total Addressable Market (TAM) for mental health²
- IDgenetix reimbursed by Medicare for major depressive disorder since 2020; recently expanded coverage for seven additional mental health conditions
- IDgenetix randomized controlled clinical-use trial demonstrated clinical utility over standard of care, when physicians used the test prior to prescribing a medication¹

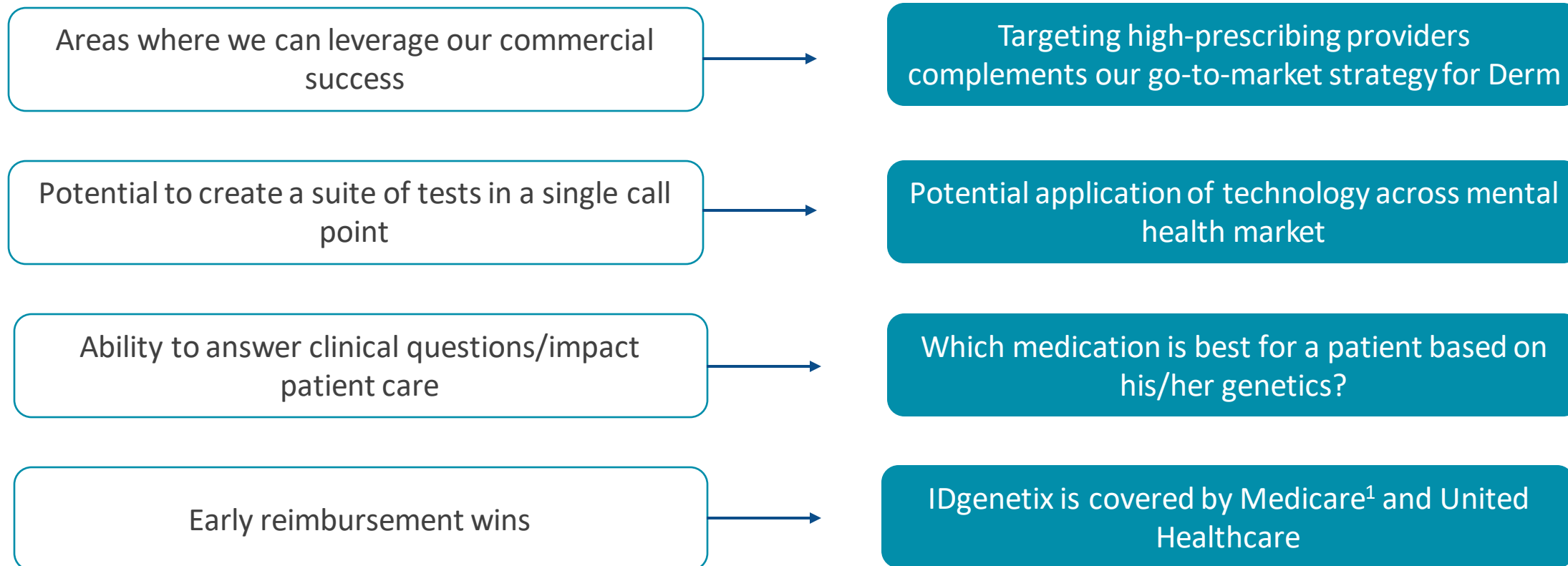
Strategic Fit

- An area where we can leverage 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

Value Rationale

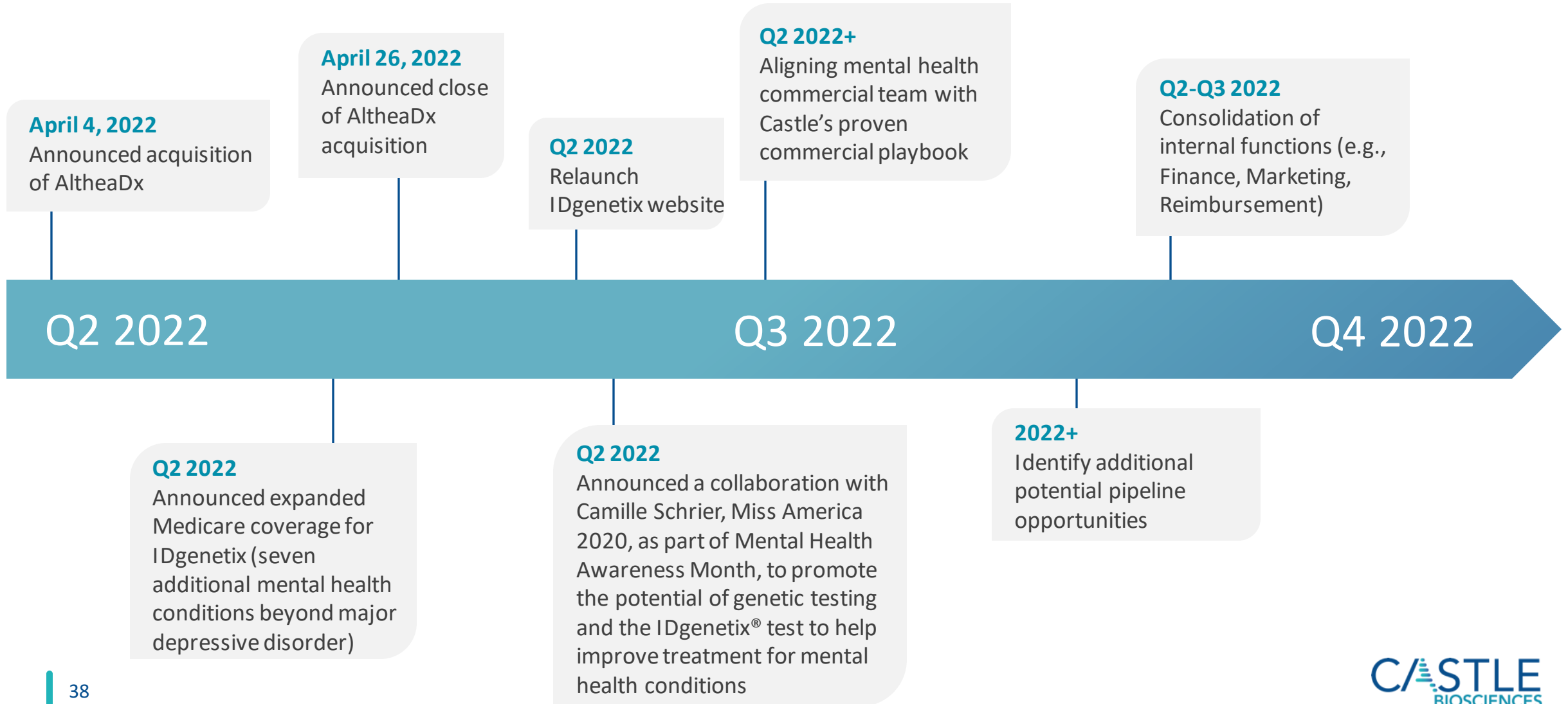
- Expands expertise into areas of mental health and treatment response through pharmacogenomic (PGx) testing
- Provides ability to build pipeline in an adjacent market (aligns with inflammatory skin disease pipeline test)
- Acquisition expected to contribute to near- and long-term revenue growth

Acquisition of AltheaDx Aligns with Castle's M&A Strategy



Our capital allocation priorities include strategic acquisitions with potential for mid- to long-term value creation and revenue and earnings growth

Mental Health/IDgenetix Integration Progress Roadmap



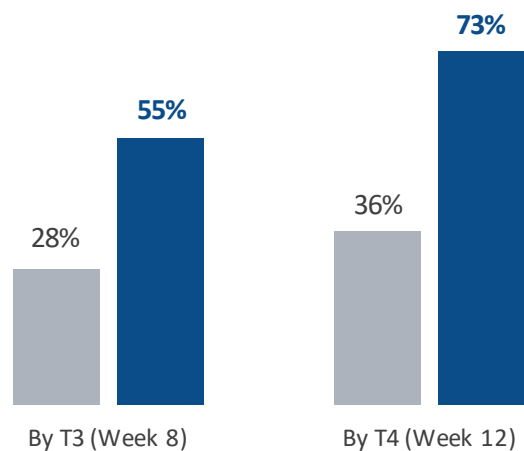
IDgenetix: Designed to Guide Timely and Evidence-Based Decisions on the Optimal Drug for Each Patient

Market Snapshot	Clinical Decision Point	Clinical Utility	Transforming Disease Management
<p>~\$5B revenue opportunity¹</p>	<p>Which medication is best for each patient?</p>	<p><i>Provides drug-gene and drug-drug interactions</i> to guide tailored treatment recommendations for patients in terms of their prescribed medications</p>	<p>Testing with IDgenetix can identify differences in a patient’s genetics as well as current medications that will impact his/her response to medications to help guide treatments that are most likely to benefit the patient and reduce risk of side effects</p> <hr/> <p>A randomized controlled trial showed that patients diagnosed with severe depression, who were assessed with the IDgenetix test, showed a greater than 2.5 times improvement in remission rates compared to those who did not have their genes tested²</p> <hr/> <p>Replacing standard-of-care, trial-and-error prescription practices in mental health with a scientifically-backed genetic test with the potential to:</p> <ul style="list-style-type: none"> • Help patients achieve a faster therapeutic response • Reduce adverse events • Yield cost savings in the healthcare system

IDgenetix provides drug-gene and drug-drug interactions

Enhanced Therapeutic Efficacy vs. Standard of Care

Response Rate ≥ 50% Reduction from Baseline



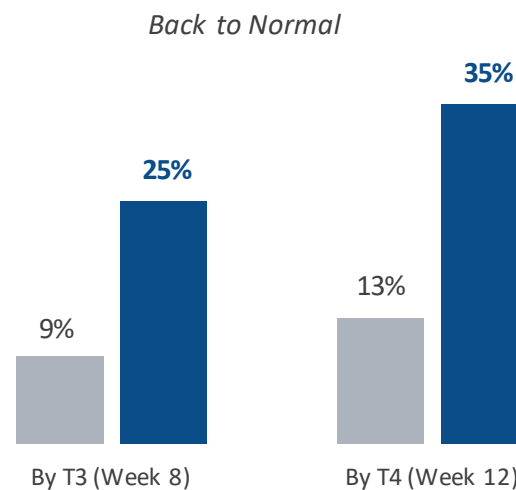
p-value

0.01

0.001

■ Control
■ IDgenetix

Remission Rate Back to Normal



p-value

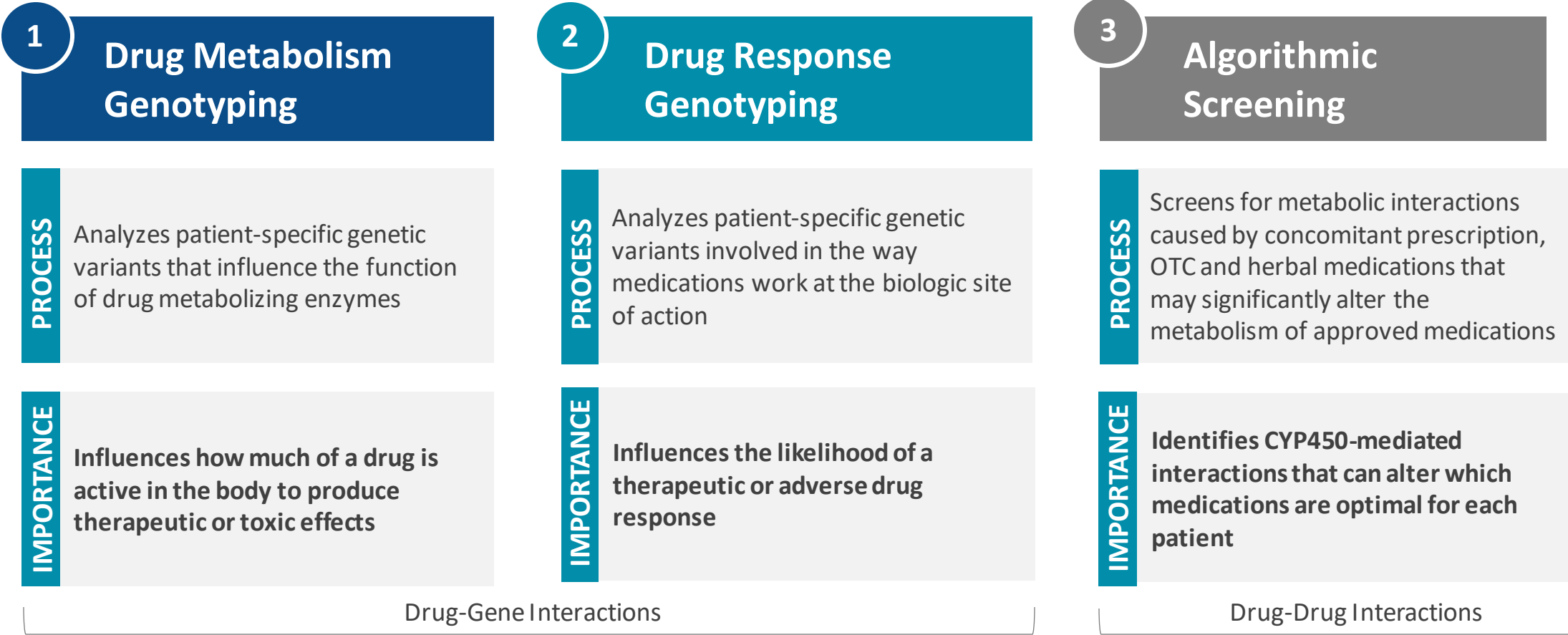
0.05

0.02

Clinical Trial Design

- Randomized Controlled Trial (RCT)
- Peer-reviewed and published in the *Journal of Psychiatric Research*
- 685 participants, Depression and Anxiety
- Double-blinded
- Treated by a broader group of medical professionals, beyond psychiatrists
- 20 independent clinical sites
- 4, 8 and 12-week efficacy using HAM-A scale

IDgenetix Testing Process Consists of Three Important Steps



IDgenetix testing is designed to provide tailored treatment recommendations for each patient by utilizing a bioinformatic algorithm to integrate patient-specific health information with comprehensive genetic results

Environmental, Social and Governance (ESG)



ESG Focus Areas for 2022 and Beyond



 Environmental policy

 Environmental metrics

 DEI mission statement

 DEI metrics

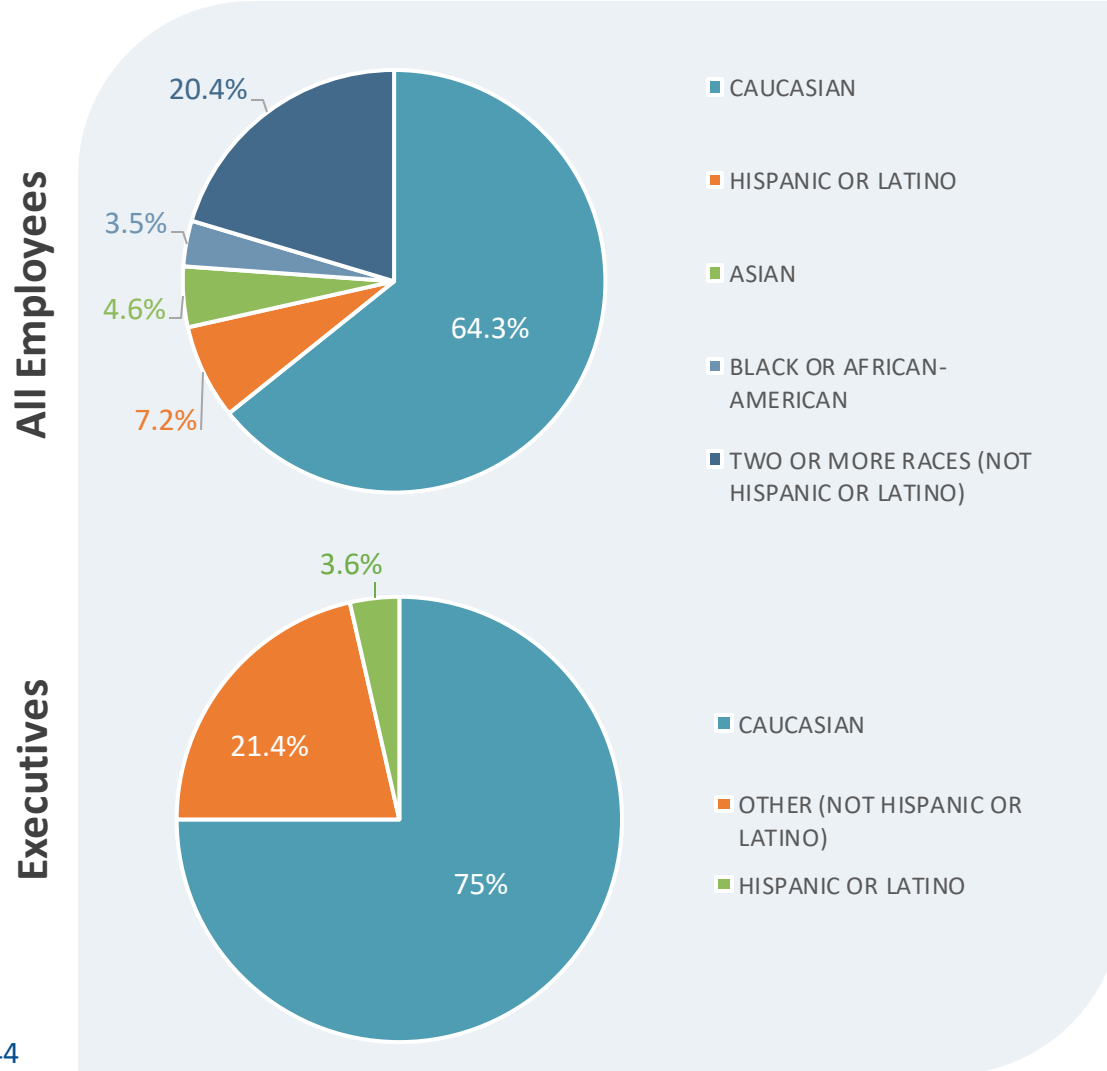
 DEI action plan/roadmap

 Vendor code of conduct/supplier standard

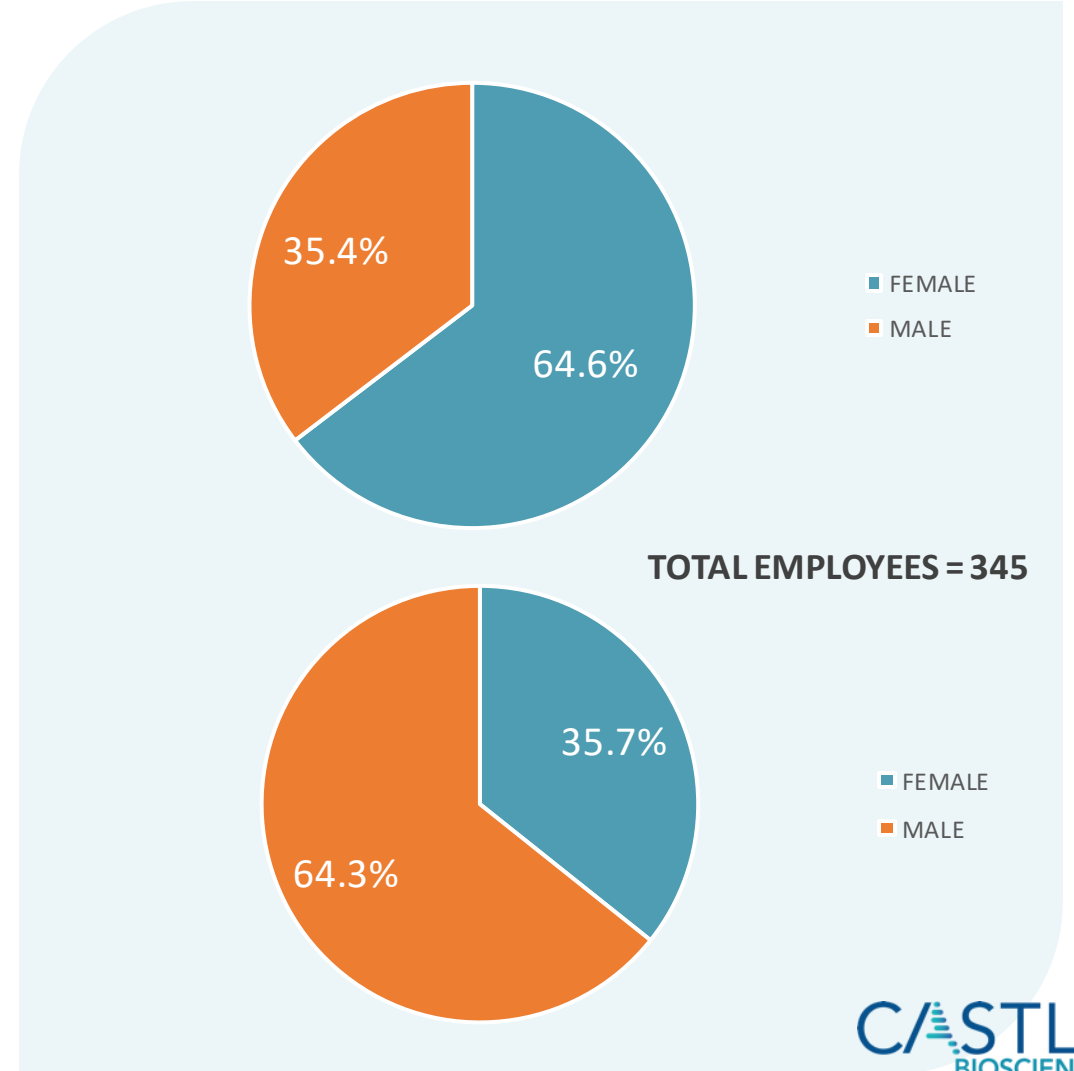


Commitment to Diversity

ETHNICITY/RACE



GENDER



C/STLE
BIOSCIENCES

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 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 GAAP basis and language from 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.

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 March 31,	
	2022	2021
<i>(in thousands)</i>		
Adjusted revenue		
Net revenues (GAAP)	\$ 26,852	\$ 22,813
Revenue associated with test reports delivered in prior periods	(602)	(5,335)
Adjusted revenue (Non-GAAP)	<u>\$ 26,250</u>	<u>\$ 17,478</u>
Adjusted gross margin		
Gross margin (GAAP) ¹	\$ 19,260	\$ 19,785
Amortization of acquired intangible assets	1,648	—
Revenue associated with test reports delivered in prior periods	(602)	(5,335)
Adjusted gross margin (Non-GAAP)	<u>\$ 20,306</u>	<u>\$ 14,450</u>
Gross margin percentage (GAAP) ²	71.7 %	86.7 %
Adjusted gross margin percentage (Non-GAAP) ³	77.4 %	82.7 %

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 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	
	March 31,	
	2022	2021
<i>(in thousands)</i>		
Adjusted operating cash flow		
Net cash used in by operating activities (GAAP)	\$ (21,430)	\$ (3,631)
HHS provider relief funds ¹	—	(1,882)
Adjusted operating cash flow (Non-GAAP)	<u>\$ (21,430)</u>	<u>\$ (5,513)</u>

¹ 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





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



Dermatology

Decision Dx
▶ Melanoma

Decision Dx
▶ SCC

MyPath | Decision Dx
Diff Dx
▶ Melanoma



Uveal Melanoma

Decision Dx
▶ UM



Gastroenterology

TissueCypher
▶ Barrett's Esophagus



Mental Health

IDgenetiX

Portfolio of innovative tests designed to guide patient care

Improving Health through Innovative Tests that Guide Patient Care

Castle Team

400 Total employees

131 Sales & marketing team members

79 Laboratory testing operations team members

77 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+ Decision Dx
▶ Melanoma

10 Decision Dx
▶ SCC

12 MyPath | Decision Dx
▶ Melanoma

22 Decision Dx
▶ UM

9 TissueCypher
▶ Barrett's Esophagus

Leadership Team Overview

MANAGEMENT TEAM

Derek Maetzold

Founder, Director, President and CEO



Frank Stokes

Chief Financial Officer



Toby Juvenal

Chief Commercial Officer



*Stuart
Pharmaceuticals*

Kristen Oelschlager, RN, CHC

Chief Operating Officer



Robert Cook, PhD

Senior Vice President, Research & Development



Northwestern



Matthew Goldberg, MD

Medical Director



Alice Izzo

Senior Vice President, Marketing



BOARD OF DIRECTORS

Dan Bradbury



Derek Maetzold



Mara Aspinall



Brad Cole



Tiffany Olson



Miles D. Harrison



Kimberlee Caple



Ellen Goldberg

CHORD Consulting



Award-Winning Company

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



**AMERICAN SKIN
ASSOCIATION**

2019 Technology Innovation in Melanoma
Award Winner