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Cernostics Acquisition

October 19, 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 expected timing and actual closing of the transaction, Castle's estimated U.S. TAM following the consummation of the transaction, Castle's ability to integrate the TissueCypher Barrett's Esophagus Assay into its commercial offerings, the ability of the Cernostics and Castle teams to complement each other and to accelerate our impact on patient care and drive value creation for shareholders, the ability of the TissueCypher Barrett's Esophagus Assay to predict future development of HGD and/or esophageal cancer in patients with BE, objectively and accurately predict progression from BE to HGD or EAC, improve the prevention of esophageal cancer and help physicians and patients make more informed management decisions based on the unique biology of individual patients' esophageal biopsies. 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 conditions to closing may not be satisfied and the transaction may be delayed or not close at all, the effects of the COVID-19 pandemic on our business and our efforts to address its impact on our business, the TissueCypher Barrett's Esophagus Assay's ability to provide the aforementioned benefits to patients, physicians and Castle and the risks set forth in our Quarterly Report on Form 10-Q for the quarter June 30, 2021, and in our other filings with the SEC. The forward-looking statements are applicable only as of the date on which they are made, and we do not assume any obligation to update any forward-looking statements, except as may be required by law.

Castle Biosciences to Acquire Cernostics

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

Fuels growth and value creation for shareholders while expanding our areas of expertise

Is aligned with our commitment to using innovative technology to answer clinical problems and guide disease management

TissueCypher platform complements our GEP dermatologic franchise, adding a first-to-market predictive test in Barrett's Esophagus

With six validation and performance studies completed, TissueCypher builds on our history of being an evidence-driven company

Opportunity to accelerate our impact on improving patient outcomes through clinically actionable precision diagnostics

Castle's Revenue Growth Story

	2021	2022	2025
Dermatologic Franchise	Cutaneous Melanoma Suspicious Pigmented Lesions	Cutaneous Melanoma Squamous Cell Carcinoma Suspicious Pigmented Lesions	Cutaneous Melanoma Squamous Cell Carcinoma Suspicious Pigmented Lesions Additional Tests for Dermatologic Conditions
	DecisionDx MELANOMA *(Expanded LCD effective Dec 2020)* ✚ myPath Melanoma *(Acquired in May 2021; LCD in effect)*	DecisionDx MELANOMA ✚ DecisionDx-SCC *(Potential LCD effective in 2022)* ✚ myPath Melanoma DecisionDx DiffDx-Melanoma *(Potential LCD effective in 2022)*	DecisionDx MELANOMA DecisionDx-SCC myPath Melanoma DecisionDx DiffDx-Melanoma ✚ **Pipeline Expansion** *(Expected launches ~2025)*
Gastrointestinal Franchise*		Barrett's Esophagus ✚ tissuecypher BARRETT'S ESOPHAGUS ASSAY	Barrett's Esophagus tissuecypher BARRETT'S ESOPHAGUS ASSAY ✚ **Pipeline Growth Opportunities**

✚Year we received/expect initial Medicare reimbursement; *Pending the closing of the Cernostics acquisition

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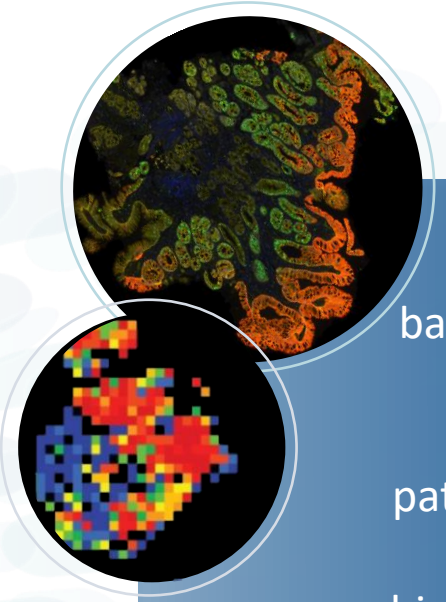
About Cernostics

Harnessing spatial biology to inform decisions in the treatment of Barrett's Esophagus



Cernostics is a leader in tissue-based diagnostic testing, delivering solutions designed to provide deeper tissue insights, better patient outcomes and lower cost of care. Cernostics applies spatial biology and biologically-aware AI to tissue diagnostics, delivering clinically actionable, precision diagnostic information to physicians and patients.

- Pittsburgh-based
- Proprietary TissueCypher (TC) platform
- First-to-market predictive test for Barrett's Esophagus (BE)
  - Six validation and performance studies
  - ~$1B estimated U.S. TAM
- Medical advisory board consists of leading GI KOLs
- GIs are receptive to the use of TC for BE patients

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Transaction and Transition Snapshot

$30 million in cash or cash and stock due at closing[1]

Up to an additional $50 million payable in cash and/or stock[1], based on the achievement of certain milestones based on 2022 performance[2]

Expected close prior to year end 2021[3]

Expect Cernostics CEO and other staff to join Castle

Expect to hire a GI commercial team with 13-15 outside sales territories; reporting to Castle's Chief Commercial Officer

[1] up to Castle's sole discretion [2]milestones related to revenue and reimbursement
[3]subject to the delivery of certain financial statements to the Company, continued employment of certain Cernostics personnel and satisfaction of other customary conditions to closing

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TissueCypher (TC) Platform Has the Potential to Answer Clinical Problems in GI and Other Diseases

Starting with TissueCypher Barrett's Esophagus Assay

The Platform

TC is designed to bring together all the key elements of biologically-aware artificial intelligence (AI) to deliver the spatialomics revolution to the clinician and enable individualized, patient-centric decision-making.

tissuecypher®
IMAGE ANALYSIS SOLUTIONS
AI Driven, Computational Pathology

How It Works

TC employs validated AI-driven algorithms designed to objectively quantify multiple biomarkers in the context of tissue structure to help physicians make more informed decisions on patient management.

Peer-Reviewed Publications

Six scientific publications support the performance of TC to objectively and independently predict the development of esophageal cancer in patients with Barrett's Esophagus.

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Patient Journey for Diagnosis and Treatment of Barrett's Esophagus (BE)

TissueCypher is indicated for BE patients with ND, IND or LGD

Patient presents to GI with severe GERD symptoms

Upper endoscopy

Results of upper endoscopy reveal	Primary treatment options
No BE (e.g., GERD)	Routine medical management
BE (~384,000 endoscopies/yr) **• Non-dysplastic (ND)** **• Indefinite for dysplasia (IND)** **• Low-grade dysplasia (LGD)**	**• EET (y/n)** **• 1x/year endoscopy** **• 3-5 years endoscopy**
BE (~16,000 endoscopies/yr) • High-grade dysplasia (HGD)	• EET • 1x/year endoscopy
Esophageal Cancer	• Surgical resection • Radiation • Therapeutics

EET=Endoscopic Eradication Therapy; which may include ablation, endoscopic mucosal resection

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Current BE Grading Systems are Limited in Predicting BE Progression

These limitations are a significant clinical issue, as BE progression risk informs treatment decisions

- High inter-observer variability
  - Observer variability caused inconsistencies in natural history studies and confusion regarding optimal management[1]
  - Variability persists among experts
- Prevalent high-grade dysplasia (HGD)/cancer can be missed on endoscopy
  - 25% of HGD/cancer diagnoses occurred within one year of endoscopy[2]
- Patients with non-dysplastic Barrett's Esophagus (ND BE) progress during surveillance intervals
- Patients with low-grade dysplasia (LGD) may be overgraded
  - 73-85% of LGDs are downgraded upon expert review[3,4]

- What is needed:
  - An objective method to improve risk-stratification in patients with BE

[1]Falk et al. *Gastroenterol Hepatol*. 2017 Apr; 13(4): 221–225; [2]Visrodia et al. *Gastroenterology*. 2016 Mar; 150 (3): 599; [3]Curvers et al. *Am J Gastroenterol*. 2010 Jul;105(7):1523. [4]Duits et al. *Gut*. 2015 May;64(5):700-6.

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TissueCypher Improves Risk-stratification in Patients Diagnosed with ND, IND or LGD Barrett's Esophagus

The problem…

Non-dysplastic 348,000 endoscopies/yr	Can progress to cancer
Indefinite 23,000 endoscopies/yr	May never progress to cancer
Low-grade dysplasia 13,000 endoscopies/yr	May never progress to cancer

The solution…

tissuecypher®
BARRETT'S ESOPHAGUS ASSAY

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TissueCypher Risk-stratifies BE Progression

Probability of developing Esophageal Cancer post endoscopy in Non-Dysplastic BE patients[1]

	Year 1	Year 5	Year 10
TissueCypher® High Risk	**1.5%**	**15.9%**	**44.8%**
Pathology – Expert	0.3%	1.9%	4.2%
Pathology – Community	0.2%	2.3%	5.0%
TissueCypher® Low Risk	**0.2%**	**1.3%**	**2.7%**

1. TissueCypher Probability in NDBE, Pathology Expert and Community in NDBE patients, prevalence adjustment constant 0.5%/year, derived from KM curves at 1, 5 and 10 years

TissueCyper **High Risk**: increased probability of progression to cancer

- 5-fold at 1 years
- 10-fold at 10 years

→

- **Increase surveillance**
- **Ablate to cure**

TissueCyper **Low Risk**: increased probability of progression to cancer

46% ↓ in probability of progression

→

- **Reduces surveillance**
- **Saves $**

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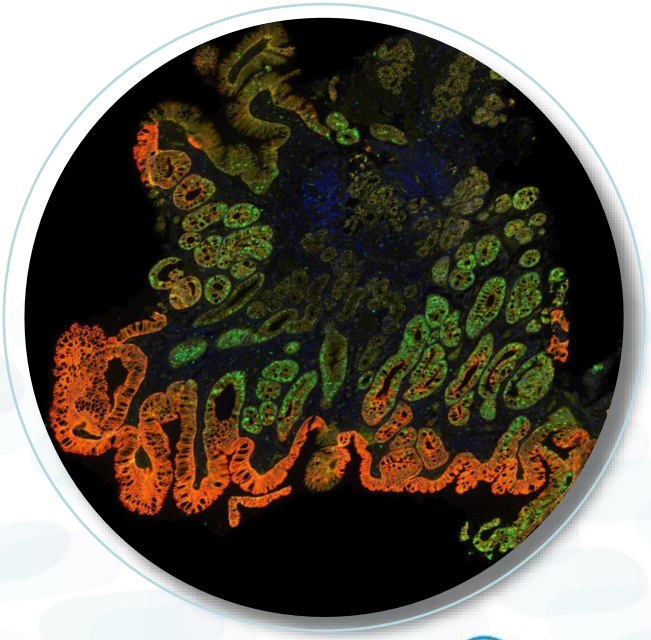
In Summary



tissuecypher®
BARRETT'S ESOPHAGUS ASSAY

- Acquisition of Cernostics brings a first-to-market risk stratification test for use in patients with Barrett's Esophagus that has
  - Significant evidence: 6 validation and performance studies with TissueCypher
  - Medicare paid with a Clinical Laboratory Fee Schedule rate of $2,513
  - Clinical use study demonstrates more than 50% change in patient management
  - Increases Castle's estimated U.S. TAM by ~$1 billion[1]
- In addition, Cernostics adds spatial biology technology for use in additional GI and other diseases

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

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THANK YOU