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Research Article

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Real World Experience and Clinical Utility of Esoguard® - Interim Data from the Lucid Registry

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Abstract

Background: *Barrett's Esophagus (BE) is the only known precursor to esophageal adenocarcinoma (EAC), but historically, screening rates have been low, likely influenced by limitations of upper endoscopy (UE) as the traditional screening modality. EsoGuard® (EG) is a DNA biomarker assay, and EsoCheck® (EC) a non-invasive, swallowable capsule device designed to collect cells from a targeted region of the esophagus. EG and EC in combination offers a well-tolerated, in-office triage test to facilitate BE detection in patients with multiple risk factors. The Lucid Registry captures real-world data from commercial use of EC with EG; we present an interim review of clinical utility data from the first 517 subjects.*

Methods: *Multicenter, prospective, registry capturing data from patients undergoing EC/EG in the commercial setting. This snapshot includes subjects enrolled from registry initiation (April 14, 2023) through August 16, 2023. The primary measure of clinical utility was provider decision impact, namely agreement between EG results and physician decision on whether to refer for subsequent UE. The relationship between BE/EAC risk factors and EG positivity rates was also assessed.*

Results: *Average age was 47.9±14.3 years, 47.2% had history of gastroesophageal reflux disease (GERD), and 63.8% had ≥3 traditional BE/EAC risk factors. 58.8% of subjects were firefighters; when firefighting was treated as an additional BE/EAC risk factor, 81.2% of the study population had ≥3. EG positivity was 14.1%. 437 subjects were followed to the clinical utility endpoint: agreement between EG (+) results and referral for UE was 100%; agreement between EG (-) results and non-referral for UE was 99.4%; concordance between EG results and UE referral was 97.9%.*

Conclusions: *Experience from the Lucid Registry demonstrates that physicians who have adopted EC/EG in the commercial setting are reliably utilizing EG as a triage test to inform decisions on which patients to refer for further endoscopic evaluation of BE.*

Keywords and Abbreviations: Barrett's Esophagus (BE), Esophageal Adenocarcinoma (EAC), Screening, Triage, EsoCheck® (EC), EsoGuard® (EG), Upper Endoscopy (UE), Clinical Utility

1. Introduction

Esophageal adenocarcinoma (EAC) is a highly lethal cancer and for whom most patients present at late stages of disease [1]. It is the most common cancer of the esophagus in the United States, with climbing numbers in the past several decades, particularly in white males, for whom incidence has increased nearly 6-fold [2-4]. National statistics estimate there will be 21,560 new cases of esophageal cancer in 2023, resulting in approximately 16,120 deaths [5]. The 5-year relative survival is estimated at 21.7%, despite treatments including surgical resection, chemotherapy, and

radiation therapy. Barrett's Esophagus (BE) is the only known direct precursor to EAC and there exist well defined risk factors that characterize a "high-risk" population to develop both conditions [6]. In contrast to EAC, BE can be successfully treated using minimally invasive approaches such as radiofrequency or cryotherapy ablation with 80-90% success rates, highlighting the importance of early diagnosis [7,8].

Despite this, literature shows less than 20% of patients in the U.S who are diagnosed with EAC have a preceding diagnosis of BE, suggesting that current screening strategies are woefully inadequate [9]. This clinical gap could be due to poor understanding from referring providers around the disease, risk factors, and its association with malignancy, and/or patient reluctance to undergo traditional screening upper endoscopy (UE), which many perceive as uncomfortable and invasive. Further, there are limitations to endoscopy with forceps biopsy as the initial approach to screening. Aside from the low rates of referral to gastroenterologists for screening UE, biopsy may miss up to 50% of BE cases due to a combination of low adherence to structured biopsy protocols, sampling error, and other factors [10]. As such, more sensitive and easier to access methods of BE detection are needed.

EsoCheck® (EC) is a non-endoscopic, swallowable, balloon-based capsule device that allows for circumferential esophageal mucosal cell sampling, and when paired with the EsoGuard® (EG) biomarker assay, offers a minimally invasive strategy recognized by both the American College of Gastroenterology (ACG) and American Gastroenterological Association (AGA) as a reasonable alternative to UE for BE screening [6,11]. EG, when used to analyze samples collected using EC, is not intended as a replacement for UE to assess known esophageal pathology. It may, however, be beneficial as a quick, easy to implement, and well-tolerated triage test that can be used in both a primary care and specialty setting to assist in the decision-making process for patients deemed at increased risk of BE. The goal of the ongoing, Lucid Diagnostics (EsoGuard) Registry (sponsored by Lucid Diagnostics Inc., New York, NY) is to collect real-world data from commercial EG experience to evaluate patient experience and satisfaction, and the impact of test results on health care provider's management decisions. All patients undergoing EG testing in the commercial setting whose cell samples were collected using EC by Lucid personnel and consented to contributing data for the Registry were included. The data presented here is for the first 517 subjects enrolled into the registry among which 437 contributed data for clinical utility assessment (provider decision impact) utilizing EG results and subsequent physician management decisions.

2. Methods

To evaluate the utility of EG as a tool in the diagnosis of BE, patient demographics, risk factors, EG results, and provider management decisions were recorded and analyzed in a prospective, observational registry. The tolerability of EC was also assessed by documenting the severity of patient gag response and the number of failed cell collections. Any patients for whom his/her physician made an independent clinical decision to screen for BE using EC/EG were invited to participate in the Lucid Diagnostics Registry. Subjects were recruited from Lucid Test Centers (LTCs), satellite testing locations, and physician, community, or employer organized health fairs/screening events from April 14th to August 16th, 2023.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the WCG Institutional Review Board (IRB tracking number 20226705). All participating individuals signed informed consent prior to EC and collection of any study information. Enrollment is ongoing and the registry is registered on clinicaltrials.gov as NCT05965999.

2.1. EsoCheck® and EsoGuard® (EC/EG)

EsoCheck® is an FDA 510K cleared, non-endoscopic, swallowable device designed for the circumferential collection and retrieval of surface cells from the esophagus (Figure 1). The unique, balloon-capsule technology allows for easy swallowing, non-traumatic targeted cell sampling, and protection of the cell sample during retrieval of the device through the upper esophagus and oropharynx. It is cleared for use in the general population of individuals 12 years of age or older.

EsoGuard® is a laboratory developed test (LDT) performed in a Clinical Laboratory Improvement Amendment (CLIA) certified and College of American Pathologists (CAP) accredited lab that utilizes set of genetic assays and algorithms which examines the presence of cytosine methylation at 31 different genomic locations on the vimentin (VIM) and Cyclin-A1 (CCNA1) genes. EG has been clinically validated in a developmental study published in 2018 and shown to have approximately 90% sensitivity and specificity in detection of disease at any stage along the BE to EAC progression spectrum [12]. EG results are reported in a binary fashion i.e., positive or negative, indicating presence or absence of sufficient methylation abnormalities to suggest diagnosis of BE or EAC. Infrequently, cell samples may have DNA "Quantity Not Sufficient" for EG analysis and are reported as "QNS," or the samples may have quality issues prohibiting analysis which are reported as "Unevaluable" If this occurs, patients have the option of repeating testing with a new cell sample.

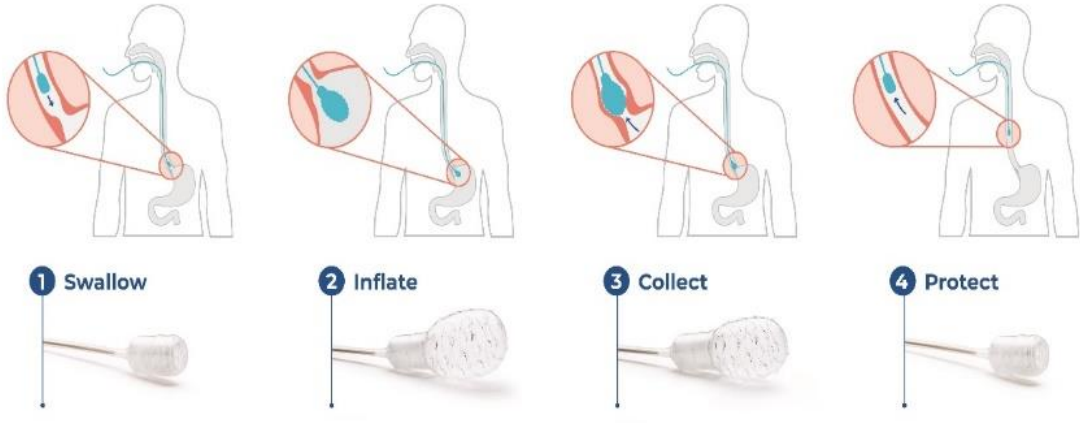

Figure 1: EsoCheck® Device and Cell Collection Process

2.2. Statistical Analysis

Subjects unable to swallow the EC device could not contribute cellular DNA for EG analysis; these subjects are included in the summary of enrollment demographics, but do not contribute to the clinical utility endpoint. Similarly, subjects without binary EG results (e.g., QNS or unevaluable) were included in overall data analysis but did not contribute to the primary clinical utility endpoints.

The primary analysis of clinical utility in this study was via provider decision impact. This was assessed as the positive agreement between EG positive (+) results and the decision to proceed with UE. Additional utility analyses included a) negative agreement between EG negative (-) results and the physician's decision not to refer for UE, and b) overall concordance between the EG result and provider endoscopy decisions. Positive agreement was calculated as the percentage of patients with EG (+) results who are referred for confirmatory UE; negative agreement was calculated as the percentage of patients with EG (-) results who are not referred for any UE.

Continuous variables were summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum, along with total number of patients contributing values. Categorical variables were described by frequency of counts and percentages. The total number of applicable subjects (N) were used as the denominator for percent calculations unless stated otherwise within a table footnote. Binomial exact two-sided 95% confidence interval were calculated wherever relevant.

3. Results

At the time of the data snapshot, 517 subjects had signed informed consent, and distribution is provided in Figure 2. One subject was pending documentation of his/her EC cell collection details and aside from demographic and BE/EAC risk factor information, was unable to contribute to data analysis. Only two individuals (2/516; 0.4%) failed to tolerate EC cell collection. Among the remaining 99.6% (514/516) who successfully completed EC to provide a cell sample for the Lab, clinical utility data was available for 437 (i.e., subjects with both binary EG results and a physician decision on UE referral); these individuals contributed to the primary and secondary endpoint analyses.

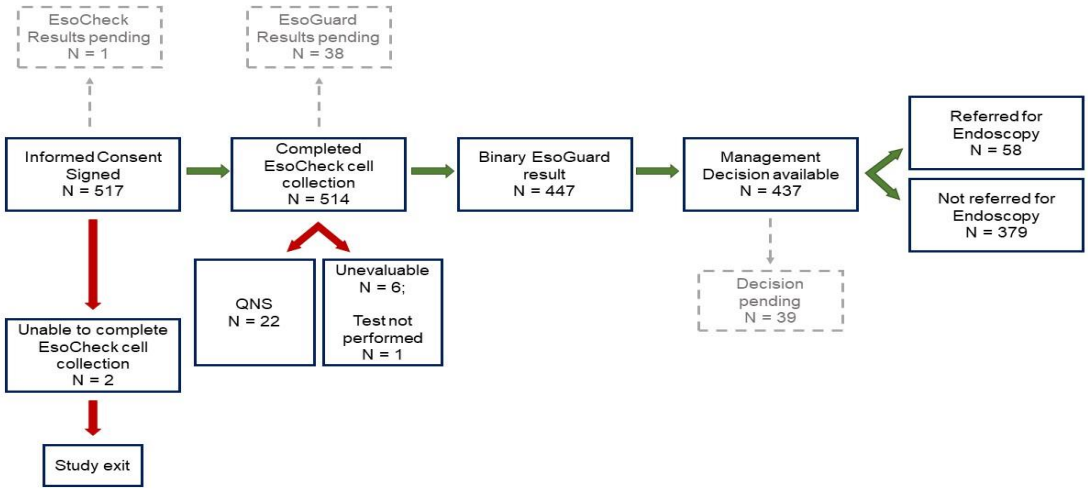

Figure 2: Subject Distribution

An overview of demographics and BE risk factors is provided in Table 1. Not all 517 enrolled subjects had complete demographic/risk information at the time of data snapshot, so analyses were performed with available datapoints. The mean age was 47.9 years (SD ± 14.3), 74.6% (385/516) were male, and 62.3% (322/517) were of White (Caucasian, non-Hispanic) race. Although <50% of subjects reported a history of gastroesophageal reflux disease (GERD), the average duration of symptoms in the GERD cohort was long, at nearly 10 years, and average symptom frequency was 3 times per week.

Characteristics	Overall (N = 517*)
Age (at time of EsoCheck cell collection; years)	
Mean ± SD	47.9±14.3 (516)
Median (Q1, Q3)	46.0 (37.0,58.0)
(Min, Max)	(20.0,88.0)
Biological Sex	
Female	25.4% (131/516)
Male	74.6% (385/516)
White (Caucasian) Non-Hispanic	
No	37.7% (195/517)
Yes	62.3% (322/517)
White (Caucasian) Hispanic	
No	69.8% (361/517)
Yes	30.2% (156/517)
Black (or African American)	
No	95.4% (493/517)
Yes	4.6% (24/517)
American Indian or Alaskan Native	
No	99.8% (516/517)
Yes	0.2% (1/517)
Asian (Asian Indian; Chinese; Filipino; Japanese; Korean; Vietnamese; Other Asian)	
No	97.3% (503/517)
Yes	2.7% (14/517)
Native Hawaiian or other Pacific Islander	
No	99.4% (514/517)
Yes	0.6% (3/517)
Cigarette Smoker (past or present)?	
No	67.5% (349/517)
Yes	32.5% (168/517)
If positive history of cigarette smoking, indicate current status:	
Current	36.3% (61/168)
Former	63.7% (107/168)
History of gastroesophageal reflux disease (GERD)?	
No	52.8% (273/517)
Yes	47.2% (244/517)
If positive history of GERD, indicate number of years with disease	
Mean ± SD	9.8±8.9 (243)
Median (Q1, Q3)	6.0 (4.0,12.0)
(Min, Max)	(0.0,50.0)
If positive history of GERD, how many times per week are symptoms experienced?	
Mean ± SD	3.1±2.2 (242)
Median (Q1, Q3)	3.0 (1.0,5.0)

(Min, Max)	(0.0,7.0)
Are GERD symptoms controlled with the acid-controlling medications?	
No	20.5% (41/200)
Yes	79.5% (159/200)
First degree family members with known diagnosis of Barrett's Esophagus (BE) and/or esophageal adenocarcinoma (EAC)?	
No	94.4% (487/516)
Yes	5.6% (29/516)
History of occupational and/or environmental exposure to agents that may increase risk of BE or EAC?	
No	41.2% (213/517)
Yes	58.8% (304/517)
Obese (defined as BMI ≥30kg/m2)	
No	64.2% (332/517)
Yes	35.8% (185/517)
Body mass index (BMI)	
Mean ± SD	29.2±5.2 (517)
Median (Q1, Q3)	28.3 (25.8,31.7)
(Min, Max)	(16.6,50.1)
AGA Cohort (3 or more ***traditional*** risk factors as defined by National Societies)	
No	36.2% (187/517)
Yes	63.8% (330/517)
AGA (+) **Cohort** (3 or more risk factors, including occupational/environmental exposure as a presumed EAC risk factor)	
No	18.8% (97/516)
Yes	81.2% (419/516)
4 or more ***traditional*** risk factors as defined by National Societies	
No	64.0% (331/517)
Yes	36.0% (186/517)
4 or more risk factors, including occupational/environmental exposure as a presumed EAC risk factor	
No	46.2% (239/517)
Yes	53.8% (278/517)
Number of Risk Factors (any)	
Mean ± SD	3.6±1.3 (514)
Median (Q1, Q3)	4.0 (3.0,4.0)
(Min, Max)	(0.0,8.0)
In addition to age >50 years, the highlighted boxes denote established/traditional risk factors as defined by National Societies *Total enrolled population N=517, among which all individuals contributed at least some demographic/risk factor information; however, not all subjects had complete information at the time of data snapshot thus the (n) in any individual row within this table may vary	

Table 1: Subject Baseline Characteristics

Patients with three (3) or more traditional risk factors for BE/EAC (referred to as the '*AGA cohort*' by our authors) accounted for 63.8% (330/517) of the Registry population. Per the AGA, such individuals are at notably increased risk for developing BE/EAC compared to the general population and therefore warrant screening. The Registry also captured information on a special category of patients: 58.8% (304/517) of participants were firefighters, as denoted by a history of "*occupational/environmental exposure to carcinogenic chemicals."*

Most of these individuals were tested as part of department or community sponsored health fairs. When "*occupational/environmental exposure to carcinogenic chemicals"* was counted as a BE/EAC risk factor, 81.2% (419/516) of the study population

had at least three (3) risk factors and met what our authors refer to as the "*AGA* (+)" criteria for BE/EAC testing (i.e., AGA-defined risk factors plus (+) occupational/environmental exposure as an added, non-traditional risk).

Characteristics	Overall (N = 517*)
Mallampati Score [13] (device administrator assessment)	
Score 1	29.1% (150/516)
Score 2	38.4% (198/516)
Score 3	24.0% (124/516)
Score 4	8.5% (44/516)
Was EsoCheck cell collection successful?	
No	0.4% (2/516) ⸸
Yes	99.6% (514/516)
Time required for cell collection (*from start of device swallowing to time of complete device retrieval; seconds*)	
Mean ± SD	104.4±71.8 (514)
Median (Q1, Q3)	60.0 (60.0,120.0)
(Min, Max)	(60.0,900.0)
Subject gag response (device administrator assessment; scale developed by and standardized among Lucid Clinical Services Staff)	
Gag Score 1 (no or minimal gagging)	36.6% (189/516)
Gag Score 2 (mild gagging)	29.8% (154/516)
Gag Score 3 (moderate gagging)	20.3% (105/516)
Gag Score 4 (severe gagging but able to complete cell collection)	13.0% (67/516)
Gag Score 5 (severe gagging and unable to complete cell collection)	0.2% (1/516)⸸
*For subjects who required more than one collection attempt, only the latest-most attempt was included in the count; one subject who was enrolled in the study (1/517) was pending documentation of his/her EsoCheck cell collection information at the time of data snapshot and thus excluded from the counts within this table. ⸸One subject who failed to swallow the EsoCheck device was documented with Gag response score <5, as the gagging was not visually assessed as severe, however the subject experienced sudden vomiting and the device was thus retrieved without adequate cell sample	

Table 2: EsoCheck Cell Collection Characteristics

3.1. EsoCheck Cell Collection Procedure

One subject was pending documentation of his/her EC cell collection information at the time of data snapshot. All except two of the other enrolled subjects (514/516; 99.6%) successfully completed the EC cell collection (Table 2). The two (0.4%) subjects unable to swallow the device and provide cell samples for EG DNA analysis were exited from the study early. The mean cell collection time was 104 seconds (1.73min), SD±71.8 seconds; the median cell collection time was 60 seconds (1 min). Most subjects had a Mallampati score of 3 or less, as assessed by the device administrator. The 'Gag response score' was a 5-point scale utilized by the device administrator to assess patient tolerability, with a score of 1 indicating the best tolerability (no or minimal gagging) and a score of 5 indicating the worst tolerability (such severe gagging that cell collection could not be completed). Most patients (448/516; 86.8%) tolerated the cell collection well, with a gag response score of 3 or less.

3.2. EsoGuard Results and Clinical Utility Evaluation

Of the 517 enrolled subjects, 476 had their EG results documented in the Registry database at the time of data snapshot (Table 3). Of note, more EG results may have been reported by the Central Lab to the ordering provider(s) but delayed data entry into the Registry database accounts for some discrepancies between the number of subjects in Table 1 compared to Table 3. The EG positivity rate was 14.1% (67/476), and 79.8% (380/476) of patients were EG negative, 4.6% (22/476) of subjects who had insufficient DNA quantity in their cell samples for analysis (QNS), and 1.3% (6/476) of samples were Unevaluable due to quality failure. One sample (0.2%; 1/476) was not yet analyzed due to administrative or other sample issues. This resulted in 93.9% (447/476) of samples with binary EG results.

Characteristics	Overall (N = 517)
EsoGuard Result*	
Positive	14.1% (67/476)
Negative	79.8% (380/476)
Not performed by Lucid Dx Lab due to administrative or sample issues	0.2% (1/476)
DNA quantity not sufficient for analysis (QNS)	4.6% (22/476)
Unevaluable cell sample	1.3% (6/476)
Was the patient referred for specialist consultation and/or upper endoscopy?⸸	
No	86.7% (379/437)
Yes	13.3% (58/437)

*At the time of data snapshot, some EsoGuard results may have been reported by Lucid Dx Lab to the ordering physician but had not yet been reviewed and/or entered in the study database; the data included in this table is not reflective of the results available at the Lab, but rather the results that were documented by study staff, which accounts for 476 of 517 total enrolled subjects

⸸At the time of data snapshot, not all physicians who had reviewed the EsoGuard results had yet reported their decision on upper endoscopy referral to study staff; information on physician referral decision was available for 437 of 517 enrolled subjects

Table 3: EsoGuard Result & Physician Decisions on Upper Endoscopy Referral

Referral decisions based on subject risk cohort: AGA vs. AGA (+) are summarized in Table 4. A decision from the ordering physician about specialist/UE referral was available for 437 subjects. In addition to the one subject for whom the EG assay was not performed due to administrative/other sample issues, there were two subjects with unevaluable samples, and 14 subjects with QNS results who did not have a decision on UE referral, likely due to anticipation of EG re-test. Among the subjects with binary EG results, 409 (55 positive, 354 negative) had physician decisions on specialist/UE referral.

Physician Decision on UE Referral	Overall		Positive		Negative		QNS		Unevaluable	
% (n/N)	95% CI	% (n/N)	95% CI	% (n/N)	95% CI	% (n/N)	95% CI	% (n/N)	95% CI	
Full Study Cohort (n = 475)										
Not referred	86.7% (378/436)	[83.1%, 89.7%]	0.0% (0/55)	[0.0%, 6.5%]	99.4% (352/354)	[98.0%,99.9%]	100.0% (21/21)	[83.9%,100.0%]	83.3% (5/6)	[35.9%,99.6%]
Referred	13.3% (58/436)	[10.3%, 16.9%]	100.0% (55/55)	[93.5%, 100.0%]	0.6% (2/354)	[0.1%,2.0%]	0.0% (0/21)	[0.0%,16.1%]	16.7% (1/6)	[0.4%,64.1%]
Cohort meeting AGA screening criteria∴ (n = 294*)										
Not referred	84.1% (217/258)	[79.1%,88.3%]	0.0% (0/38)	[0.0%,9.3%]	99.0% (202/204)	[96.5%,99.9%]	100.0% (14/14)	[76.8%,100.0%]	50.0% (1/2)	[1.3%,98.7%]
Referred	15.9% (41/258)	[11.7%,20.9%]	100.0% (38/38)	[90.7%,100.0%]	1.0% (2/204)	[0.1%,3.5%]	0.0% (0/14)	[0.0%,23.2%]	50.0% (1/2)	[1.3%,98.7%]
Cohort meeting AGA(+) screening criteria∴ (n = 377)										
Not referred	84.9% (287/338)	[80.6%,88.6%]	0.0% (0/48)	[0.0%,7.4%]	99.3% (269/271)	[97.4%,99.9%]	100.0% (15/15)	[78.2%,100.0%]	75.0% (3/4)	[19.4%,99.4%]
Referred	15.1% (51/338)	[11.4%,19.4%]	100.0% (48/48)	[92.6%,100.0%]	0.7% (2/271)	[0.1%,2.6%]	0.0% (0/15)	[0.0%,21.8%]	25.0% (1/4)	[0.6%,80.6%]

*36 out of 330 subjects within this risk cohort were pending UE referral decisions at the time of data snapshot

⸸42 out of 419 subjects within this risk cohort were pending UE referral decisions at the time of data snapshot

∴Some, but not all subjects in the AGA(+) risk cohort also fell within the AGA risk cohort, whereas all subjects in the AGA risk cohort also met criteria for the AGA(+) cohort

Table 4: EsoGuard Results and Decisions on Endoscopy Referral by Risk Cohort

Analysis Set	Subjects with Binary EG Result and a physician decision on UE referral (N)	Positive Agreement* (95% CI)	Negative Agreement⸸ (95% CI)	Concordance (95% CI)⸸
Overall	409	100.0% (93.5%,100.0%)	99.4% (98.0%,99.9%)	97.9% (95.1%,100.0%)

AGA Cohort	242	100.0% (90.7%,100.0%)	99.0% (96.5%,99.9%)	96.9% (92.7%,100.0%)
AGA(+) Cohort	319	100.0% (92.6%,100.0%)	99.3% (97.4%,99.9%)	97.6% (94.3%,100.0%)
Cohort with 4 or more ***traditional*** risk factors (*excludes occupational/environmental exposure as a risk*)	139	100.0% (88.8%,100.0%)	98.1% (93.5%,99.8%)	95.9% (90.4%,100.0%)
Cohort with ≥4 risk factors for BE ***including occupational/ environmental exposure***	207	100.0% (90.3%,100.0%)	98.8% (95.8%,99.9%)	96.7% (92.2%,100.0%)
*Primary Clinical Utility Endpoint ‡Secondary Clinical Utility Endpoint				

Table 5: Primary Clinical Utility Endpoint(s) by Risk Category

All individuals with EG positive results were referred for UE, irrespective of whether patients were in the AGA risk cohort vs. 'AGA (+)' risk cohort. Only two subjects with a negative EG result were referred for UE – all others did not undergo further diagnostic work-up. Both subjects were from the AGA risk cohort. The primary clinical utility endpoint was calculated for subjects who had both a binary EG result and a physician decision on UE referral (Table 5). The positive agreement between an EG (+) test result and decision to refer the subject to specialist and/or UE was calculated at 100%, which was consistent across all cohorts. The Negative agreement for the full study population was 99.4%, which was nearly identical for the AGA and AGA (+) cohorts at 99.0% and 99.3% respectively. For subjects with ≥4 BE/EAC risk factors, the negative agreement was >98%. Overall concordance between EG result and physician decision on UE referral was 97.9%.

Characteristics	**Overall (N = 475)**	**EG Positive (N = 67)**	**EG Non-Positive* (N = 408)**	**p-Value**
Age (years)				
Mean ± SD	47.5±14.2 (474)	57.8±14.1 (67)	45.8±13.5 (407)	<.001
Median (Q1, Q3)	46.0 (36.0,57.0)	56.0 (46.0,68.0)	45.0 (35.0,54.0)	
(Min, Max)	(20.0,88.0)	(22.0,88.0)	(20.0,81.0)	
Number of Risk Factors (any, ***including*** *occupational/ environmental exposure*)				
Mean ± SD	3.6±1.3 (472)	4.1±1.3 (67)	3.5±1.3 (405)	<.001
Median (Q1, Q3)	4.0 (3.0,4.0)	4.0 (3.0,5.0)	3.0 (3.0,4.0)	
(Min, Max)	(0.0,8.0)	(0.0,7.0)	(0.0,8.0)	
AGA Cohort (3 or more traditional risk factors) N=330				0.021
No	38.1% (181/475)	25.4% (17/67)	40.2% (164/408)	
Yes	61.9% (294/475)	74.6% (50/67)	59.8% (244/408)	
AGA (+) **Cohort** (3 or more risk factors; includes *occupational/environmental exposure as a risk*) N=419				0.028
No	20.5% (97/474)	10.4% (7/67)	22.1% (90/407)	
Yes	79.5% (377/474)	89.6% (60/67)	77.9% (317/407)	
Cohort with 4 or more ***traditional*** risk factors (excludes *occupational/environmental exposure as a risk*) N = 186				<.001
No	65.1% (309/475)	46.3% (31/67)	68.1% (278/408)	
Yes	34.9% (166/475)	53.7% (36/67)	31.9% (130/408)	
Cohort with ≥4 risk factors for BE ***including occupational/ environmental exposure*** N = 278				0.009
No	47.6% (226/475)	32.8% (22/67)	50.0% (204/408)	
Yes	52.4% (249/475)	67.2% (45/67)	50.0% (204/408)	

*Includes subjects who were either EG(-) or are pending EG results but have undergone successful EC cell collection and provided complete demographic/risk factor information

Table 6: Comparison of Characteristics Between EsoGuard Positive vs Negative Subjects

When comparing characteristics of EG (+) vs. EG (-) subjects, there was a statistically significant difference in age and number of BE/EAC risk factors (Table 6). In general, the EG positive subjects were older (mean age of 57.8 years) and had more risk factors (average of 4.1) compared to EG negative subjects (mean age of 45.8 years and average 3.5 risk factors). Of similar statistical significance was the finding that EG positive patients were more likely than EG negative subjects to have ≥4 traditional BE risk factors.

4. Discussion

BE is the only known precursor to EAC, however, most cases of EAC are found in individuals without an established BE diagnosis, which means the window for early detection of the precancerous condition (BE) and intervention to prevent malignant progression was missed [14-16]. There is evidence to suggest that patient factors and endoscopy access issues are contributory to poor rates of screening. Kolb et. al. utilized web-based surveys to collect information from GERD patients around how they perceive BE risk and the benefits of screening. About one fifth (20.4%) of patients admitted fear of discomfort as a barrier to undergoing screening UE, along with logistical considerations (e.g., scheduling, location, wait time, post-sedation/post-anesthesia needs etc.,); this concern was increased among patients who had never undergone a prior UE [17]. This suggests that non-endoscopic solutions such as EsoCheck and EsoGuard (EC/EG) could potentially improving acceptability and accessibility of BE testing among individuals who might otherwise be unable or unwilling to comply with traditional diagnostic evaluation.

EC/EG, was developed as a triage tool in the diagnosis of patients with BE; although data also demonstrates excellent ability to detect EAC, the intent is early detection of BE (i.e., pre-malignant disease), which then allows appropriate surveillance or treatment, with the ultimate goal of halting progression to malignancy [12]. As a triage tool, EC/EG would be performed as a first step in the diagnostic work-up, with the results informing the next steps in patient management. The intended use population for EC/EG is not a general screening population, as there are well-established risk factors associated with development of BE and EAC. Instead, this solution is intended for testing patients with multiple risk factors. It is also not intended to replace UE in patients with concerning symptoms that would warrant UE for non-screening purposes (e.g., new, or worsening dysphagia, refractory GERD symptoms, etc.). In 2022 the AGA published their Clinical Practice Update on New Technology and Innovation for Surveillance and Screening of BE, in which they recommended screening for individuals with at least three established/traditional risk factors and endorsed non-endoscopic cell collection paired with a biomarker test as a reasonable alternative to UE as an initial test.

When the EG (+) vs. EG (-) populations within the Lucid Registry were compared, in general, the EG positive subjects were older and had more risk factors compared to EG negative subjects. Overall, 63.8% of individuals had risk characteristics aligned with AGA recommendations for BE screening, and 81.2% of participants met what the authors refer to as "AGA (+)" criteria, meaning they had three or more risk factors for BE/EAC when counting occupation as a firefighter (with frequent environmental exposure to smoke and other carcinogenic compounds) as a risk factor. The occupation of firefighting is known to increase an individual's likelihood of developing a multitude of malignancies including esophageal cancer and was designated a Group 1 carcinogen by the International Agency for Research on Cancer (IARC) in July of 2022 [18]. While not included in current society guidelines as a traditional risk factor for BE/EAC, an increased incidence of esophageal cancer-related deaths in firefighters – most frequently EAC - is demonstrated in the literature and likely attributable to their ongoing exposure to smoke and other toxic agents [19,20]. In a study of California firefighters, the odds ratio (OR) for development of EAC in those of White race was 1.84, and 1.85 for firefighters of any race [21]. This is comparable to the association between BE and central obesity, with an OR of 1.88 when adjusted for BMI, and OR of 1.98 when unadjusted for BMI [22].

The EC cell collection process was shown to be efficient and highly successful; only two of 516 subjects (0.4%) were unable to swallow the device and average cell collection time was less than two minutes (104.4 seconds). Tolerability, as assessed by the patient's 'Gag response score' was generally good, with most subjects (86.5%) evaluated to have a gag score of 3 (moderate gag) or less; a score of only 1 (no gag or minimal gag) was seen in over a third of the population (Table 2). The EG positivity rate for the Lucid Registry population (14.1%) aligns well with incidence of BE from the literature in a multi-risk factor population, which ranges between 5-15% [23]. When we evaluated the AGA risk cohort and the "AGA (+)" cohorts separately, we saw that positivity rates were similar, at 15.1% (50/330) and 14.3% (60/419) respectively. Although data comparing EG results to endoscopy findings is outside the scope of this Clinical Utility discussion, the consistency between EG positivity rates and published disease prevalence is overall reassuring.

The clinical utility of a triage test is derived from its ability to guide provider decision-making – generally on next steps in diagnostic evaluation and/or management. As such, for our analysis of the Lucid Registry data, clinical utility of EC/EG was assessed based its impact on provider decision(s) to refer or not refer their patient(s) for confirmatory upper endoscopy. 100% of Registry patients with positive EG results were referred for confirmatory UE, while only two EG negative subjects (2/354, 0.6%; Table 4) were referred. The 100% agreement between EG (+) results and UE referral demonstrates that ordering physicians view positive biomarker test results as actionable. Perhaps more importantly, the >99% agreement between EG (-) results and decision not to refer for UE reflects physician confidence in the

ability of EG to appropriately capture any patients with disease. It suggests physicians are sufficiently reassured by a negative result to not waste resources on further invasive diagnostic evaluation. Overall, this concordance between EG results and UE referral behaviors suggests there is appropriate utilization of EG as a triage test in the real-world setting.

Patient compliance with endoscopy referrals was not included within this data snapshot and may be viewed as a limitation; such data is in the process of being captured within the Registry database and will be presented in future publications. Given the timing of the data snapshot and the relatively long lead-time required to schedule and undergo endoscopy, this information was mostly unavailable for the current analysis. As discussed previously, the delays and difficulties associated with scheduling UE are factors contributing to poor patient acceptance of this procedure as an initial BE screening test. Details about the individual EG ordering providers were not collected, nor included in this analysis. This may be considered an additional limitation, however, it can be assumed that ordering providers are diverse in respect to geography, specialty (consisting of primary care providers, gastroenterologists, foregut surgeons, and laryngoscopists), and consist of both academic and non-academic practices, as this is what's seen in the overall Lucid Diagnostics commercial market. Indeed, most commercial clients are from non-academic institutions in non-urban areas, which is reflective of the overall mission of this technology to increase accessibility of BE testing outside regions/practices where UE is most readily available as a screening tool.

In short, preliminary review of real-world data collected from the Lucid Diagnostics Registry demonstrates that providers are reliably utilizing the test as a triage tool to guide determination of which patients to refer or not refer for endoscopic evaluation of BE. This approach could enable broader outreach and more consistent testing of increased-risk patients, while also focusing UE resources on those patients with the highest pre-procedure probability of disease.

5. Conclusions

Experience from the Lucid Diagnostics (EsoGuard) Registry demonstrates that physicians who have adopted EC/EG in the commercial setting are reliably utilizing EG to inform decision making on which patients to refer for further endoscopic evaluation of BE. This strategy may be an effective method for ensuring that more high-risk individuals are undergoing diagnostic testing, while also tailoring UE resource utilization.

Author Declaration

The authors attest this work has not been published before (except in the form of a pre-print on MedRxiv, https://www.medrxiv.org/) and is not under consideration for publication elsewhere.

Conflicts of Interest

Authors Richard Englehardt, Jason B Samarasena, Nikolai A Bildzukewicz and Rachelle Hamblin declare no specific conflicts of interest. Authors Victoria T Lee, Brian J deGuzman, Suman Verma and Lishan Aklog are executive members of Lucid Diagnostics Inc., and own stock and/or options in the company.

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