Real-World Health Disparities in Time to Next Treatment Following First-Line Therapy for Advanced and Recurrent Endometrial Cancer in the United States

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Introduction

- The incidence of endometrial cancer (EC) in the United States (US) has continued to increase over the past 25 years, with persistent disparities for African American and Black women that are projected to widen[1]
- Notably, Black women are projected to continue to experience a disproportionate increase in incidence (ie, incidence rates per 100,000 almost doubling[2]) demonstrating substantial and widening racial disparities
- Prior studies have consistently demonstrated that Black women with EC experience higher mortality compared with White women, despite similar incidence rates[1]
- Differences in tumor biology and stage at diagnosis in part may explain these disparities: Black women are more frequently diagnosed with aggressive histologic subtypes (eg, nonendometrioid) and present with advanced-stage disease, which are associated with poorer prognosis and worse response to standard therapies[3,4]
- This disparity persists after accounting for factors such as age, comorbidity burden, disease stage, and health care settings with equal access to care (eg, the US Military Health System)[1,3,5,6]
- Assessing differences in time to next treatment, a surrogate for progression-free survival,[7] helps to understand these potential disparities in treatment effectiveness by race

Objectives

- Describe the differences in sociodemographic and clinical characteristics stratified by race among women with advanced or recurrent endometrial cancer who initiated first-line (1L) systemic therapy
- To examine the differences in real-world time to next treatment (rwTTNT), a surrogate for progression-free survival,[7] to understand disparities in treatment effectiveness by race

Methods

Design

- Study design: retrospective cohort study between January 1, 2013, and June 30, 2025
- Data source: Flatiron is a nationwide database of longitudinal electronic health records, comprising deidentified structured and unstructured data from ~280 cancer care entities and 800 clinical care sites, including both community and academic oncology practices[8]
- Study population: women aged ≥18 years with aEC who initiated 1L therapy between January 1, 2013, and June 30, 2025 (see **Figure 1** for study cohort attrition)

Measures

- *Outcomes:* rwTTNT, defined as the time from the start of 1L treatment to the initiation of second-line (2L) treatment or death, whichever occurs first
- *Sociodemographic characteristics:* age, race, ethnicity, geographical region of the US, socioeconomic status (SES), practice setting, and insurance type
- *Clinical characteristics:* body mass index (BMI), de novo/recurrent status, Eastern Cooperative Oncology Group (ECOG) performance score, Charlson comorbidity index (CCI), histology, 1L initiation before/after 2023 National Comprehensive Cancer Network (NCCN) guidelines update, and tumor mismatch repair (MMR)/microsatellite instability (MSI) status

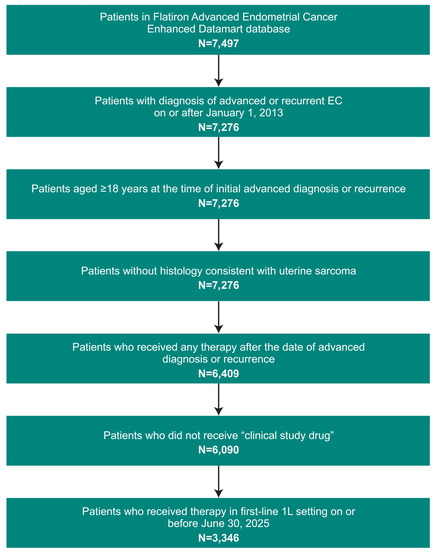
Analyses

- Baseline demographic and clinical characteristics were summarized using descriptive statistics and stratified by race
- Kaplan-Meier (KM) curves estimated rwTTNT by race
- After the proportional hazard assumption was found to be violated using scaled Schoenfeld residuals and a chi-square test, an accelerated failure time (AFT) regression was chosen to model the time-to-event analyses
  - First, an appropriate parametric distribution was needed to fit the curve. Model selection (eg, log-likelihood, AIC, BIC) and goodness-of-fit tests (eg, Kolmogorov-Smirnov, Anderson-Darling), as well as visual inspection of the fitted curves, guided this decision
- Time ratios (TRs), comparing for rwTTNT across racial groups, were estimated using AFT models, adjusted for sociodemographic, clinical, and tumor characteristics

Results

- A total of 3,346 women with aEC who initiated 1L therapy were included (**Figure 1**); 59% (1,963) of women were White, 18% (610) Black, 2% (71) Asian, and 21% (702) other or unknown race

Figure 1. Study cohort attrition



Cohort characteristics

- Compared to White women, Black women were more likely to live in the Southern US (51.0% vs 32.8%) and be in the lowest SES quintile (38.7% vs 12.9%) (**Table 1**)
- Black women more often had advanced disease (vs recurrent, 56.7%) compared to White women (47.5%). Black women were also more likely to have serous carcinoma (40.3% vs 24.6%), carcinosarcoma/mixed Müllerian tumors (18.0% vs 8.6%), and proficient mismatch repair (pMMR) tumors (49.8% vs 43.3%) than White women
- Overall, 50.1% of the study population received platinum + taxane as 1L treatment, roughly equivalent across racial groups
- Immunotherapy monotherapy was used as 1L treatment in 4.4% of all women, 2.9% of Black women, and 4.3% of White women
- Immunotherapy in combination with chemotherapy was the most common 1L immunotherapy regimen, used in 8.5% of all women, including 7.5% of Black and 6.2% of White women

Table 1. Sociodemographic and clinical characteristics of advanced or recurrent EC patients who initiated 1L therapy

Demographic characteristics	Overall N = 3,346 (100%)	White N = 1,963 (59%)	Black N = 610 (18%)	Asian N = 71 (2%)	Other/Unknown N = 702 (21%)
Age, years					
Median (Q1, Q3)	67.0 (61, 74)	68.0 (61, 74)	67.0 (62, 72)	63.0 (55, 72)	68.0 (60, 74)
Ethnicity, N (%)					
Hispanic or Latino	235 (7.0)	98 (5.0)	10 (1.6)	0 (0)	127 (18.1)
Not Hispanic or Latino	2,513 (75.1)	1,667 (84.9)	536 (87.9)	58 (81.7)	252 (35.9)
Unknown	598 (17.9)	198 (10.1)	64 (10.5)	13 (18.3)	323 (46.0)
BMI at 1L initiation, kg/m^2					
Median (Q1, Q3)	30.8 (25.9, 36.7)	30.96 (25.9, 37.3)	31.6 (27.1, 37.1)	23.93 (20.8, 26.8)	30.32 (25.9, 35.9)
Geographic region, N (%)					
Northeast	358 (10.7)	201 (10.2)	55 (9.0)	13 (18.3)	89 (12.7)
Midwest	356 (10.6)	264 (13.4)	45 (7.4)	10 (14.1)	37 (5.3)
South	1,212 (36.2)	644 (32.8)	311 (51.0)	12 (16.9)	245 (34.9)
West	369 (11.0)	159 (8.1)	14 (2.3)	15 (21.1)	181 (25.8)
Unknown	1,051 (31.4)	695 (35.4)	185 (30.3)	21 (29.6)	150 (21.4)
Insurance status at 1L initiation, N (%)					
Commercial health plan	754 (22.5)	460 (23.4)	126 (20.7)	22 (31.0)	146 (20.8)
Commercial health plan – Medicare	1,182 (35.3)	737 (37.5)	225 (36.9)	15 (21.1)	205 (29.2)
Medicaid/Medicare/other government program	592 (17.7)	348 (17.7)	112 (18.4)	13 (18.3)	119 (17.0)
Other payer – type unknown	97 (2.9)	47 (2.4)	20	7 (9.9)	23 (3.3)
Patient assistance program/self-pay	39 (1.2)	27 (1.4)	5	0 (0)	11 (1.6)
Uninsured/insurance not documented	682 (20.4)	344 (17.5)	126 (20.7)	14 (19.7)	198 (28.2)
Socioeconomic status index, N (%)					
1 (lowest)	631 (18.9)	253 (12.9)	236 (38.7)	≤10	137 (19.5)
2	580 (17.3)	345 (17.6)	112 (18.4)	≤10	115 (16.4)
3	605 (18.1)	361 (18.4)	91 (14.9)	16 (22.5)	137 (19.5)
4	656 (19.6)	431 (22.0)	70 (11.5)	17 (23.9)	138 (19.7)
5 (highest)	549 (16.4)	377 (19.2)	42 (6.9)	21 (29.6)	109 (15.5)
Unknown	325 (9.7)	196 (10.0)	59 (9.7)	≤10	66 (9.4)
Histology at advanced/recurrent diagnosis, N (%)					
Endometrioid carcinoma	1,539 (46.0)	1,021 (52.0)	166 (27.2)	40 (56.3)	312 (44.4)
Carcinosarcoma/MMT	366 (10.9)	169 (8.6)	110 (18.0)	7 (9.9)	80 (11.4)
Clear cell carcinoma	137 (4.1)	79 (4.0)	26 (4.3)	≤5	29 (4.1)
Serous carcinoma	945 (28.2)	483 (24.6)	246 (40.3)	16 (22.5)	200 (28.5)
Endometrial cancer, NOS	359 (10.7)	211 (10.7)	62 (10.2)	≤5	81 (11.5)
Advanced/recurrent status, N (%)					
Advanced	1,705 (51.0)	932 (47.5)	346 (56.7)	34 (47.9)	393 (56.0)
Recurrent	1,641 (49.0)	1,031 (52.5)	264 (43.3)	37 (52.1)	309 (44.0)
ECOG at 1L initiation, N (%)					
0-1	1,644 (49.1)	959 (48.9)	314 (51.5)	38 (53.5)	333 (47.4)
2-4	364 (10.9)	213 (10.9)	60 (9.8)	6 (8.5)	85 (12.1)
Missing	1,338 (40.0)	791 (40.3)	236 (38.7)	27 (38.0)	284 (40.5)
MMR/MSI at any time before 1L initiation, N (%)					
dMMR and/or MSI-H	470 (14.0)	305 (15.5)	58 (9.5)	10	97 (13.8)
pMMR and/or MSS	1,511 (45.2)	849 (43.3)	304 (49.8)	40 (56.3)	318 (45.3)
Discordant	41 (1.2)	26 (1.3)	5 (0.8)	0 (0)	10 (1.4)
Other	87 (2.6)	47 (2.4)	47 (2.4)	5	22 (3.1)
Missing	1,237 (37.0)	736 (37.5)	736 (37.5)	20 (28.2)	255 (36.3)
Time from diagnosis to 1L initiation, months					
Median (Q1, Q3)	1.45 (0.72, 2.89)	1.41 (0.72, 2.92)	1.38 (0.76, 2.66)	1.48 (0.76, 2.73)	1.61 (0.79, 3.06)
Length of follow-up from 1L initiation, months					
Median (Q1, Q3)	18.42 (7.66, 47.28)	19.68 (8.05, 52.53)	16.05 (7.13, 36.53)	17.94 (7.59, 49.38)	18.52 (7.33, 47.28)
Range	(0, 157.6)	(0, 146.9)	(0, 157.6)	(0.9, 146.9)	(0, 146.9)
1L treatment regimen, N (%)					
Platinum + taxane	1,675 (50.1)	978 (49.8)	329 (53.9)	35 (49.3)	333 (47.4)
Immune checkpoint inhibitor monotherapy	147 (4.4)	88 (4.5)	16 (2.6)	5	40 (5.7)
Immune checkpoint inhibitor + platinum + taxane	286 (8.5)	133 (6.8)	58 (9.5)	10	85 (12.1)
1L initiation before March 2023, N (%)					
Yes	2,671 (79.8)	1,601 (81.6)	490 (80.3)	53 (74.6)	527 (75.1)
No	675 (20.2)	362 (18.4)	120 (19.7)	18 (25.4)	175 (24.9)
Practice Setting, N (%)					
Academic	767 (22.9)	526 (26.8)	148 (24.3)	20	75 (10.7)
Community	2,493 (74.5)	1,377 (70.1)	455 (74.6)	51 (71.8)	610 (86.9)
Both	86 (2.6)	60 (3.1)	7 (1.1)	5	17 (2.4)
CCI, N (%)					
0	522 (15.6)	318 (16.2)	90 (14.8)	10	≤105
1	30 (0.9)	13 (0.7)	14 (2.3)	5	5
2	1,298 (38.8)	690 (35.2)	236 (38.7)	34 (47.9)	338 (48.1)
3+	1,496 (44.7)	942 (48.0)	270 (44.3)	26 (36.6)	258 (36.8)

MMT, mixed Müllerian tumor, MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NOS, not otherwise specified.

Real-world time to 2L therapy

- The Kaplan-Meier curve indicated that median rwTTNT was lower among Black women (7.2 months) than White women (8.0 months) (**Figure 2**)
  - 12 months without initiation of 2L, 29.5% (Black) vs 36.8% (White)
  - 24 months without initiation of 2L, 12.8% (Black) vs 21.2% (White)

Tests for proportionality and AFT parametric distribution selection

- The proportionality assumption was assessed using scaled Schoenfeld residuals and a chi-square test. The results showed that several covariates included in the TTNT Cox model violated the proportional hazards assumption, indicating that a standard Cox model may not be appropriate
- For the parametric distribution selection, model selection tests and goodness-of-fit tests were used, where the lower values indicate a better fit
- As seen in **Table 2**, for the model selection tests, general gamma performed best. For goodness-of-fit, log-normal distribution was superior
- The general gamma and log-normal distributions performed best following the formal tests, a final decision was made using visual inspection of the data
- The log-normal distribution (**Figure 2**) was slightly closer to the observed distribution than the general gamma (**Figure 3**), therefore a log-normal AFT regression was used for TTNT.

Table 2. Model selection and goodness-of-fit tests for identification of parametric distribution for the accelerated failure time model

Model	Model selection tests			Goodness-of-fit tests		
	Log-likelihood	AIC	BIC	Kolmogorov-Smirnov	Anderson-Darling	Cramér–von Mises
Exponential	9,825.56	19,743.12	20,024.43	0.1755	218.26	46.76
General gamma	9,541.92	19,179.84	19,473.39	0.1168	81.59	15.4
Log-normal	9,547.31	19,188.62	19,476.05	0.1144	80.66	14.47
Weibull	9,714.02	19,522.05	19,809.48	0.1429	119.18	25

Figure 2. Fitted values of the log-normal distribution vs. the observed distribution

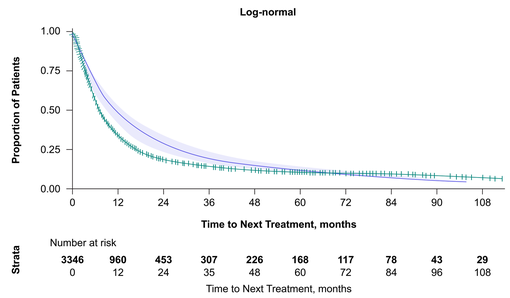
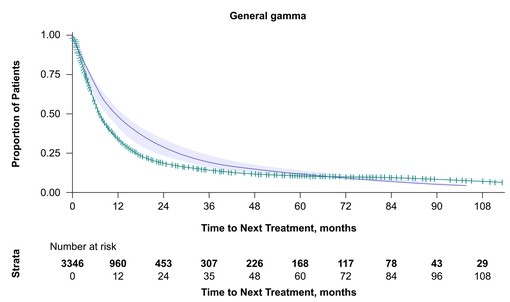


Figure 3. Fitted values of the general gamma distribution vs. the observed distribution



Adjusted time ratios

- After adjustment, Black women had significantly shorter rwTTNT, a 15% lower time to 2L therapy compared to White women (TR = 0.85; 95% CI, 0.74-0.99)
- When compared to endometrioid carcinoma, other histologies were associated with shorter rwTTNT, including:
  - Serous carcinoma: TR = 0.81 (95% CI, 0.71-0.92)
  - Carcinosarcoma/mixed Müllerian tumor: TR = 0.67 (95% CI, 0.57-0.80)
- Proficient MMR (pMMR)/microsatellite stable (MSS) tumors were associated with shorter rwTTNT (TR = 0.80; 95% CI, 0.68-0.95 vs deficient MMR [dMMR]/microsatellite instability-high [MSI-H] tumors)
- Poorer ECOG performance scores were associated with shorter rwTTNT (relative to scores of 0-1)
  - ECOG performance scores of 2-4: TR = 0.55 (95% CI, 0.47-0.65)
- Overweight and obesity were associated with longer rwTTNT (as compared to normal BMI):
  - Overweight: TR = 1.27 (95% CI, 1.09-1.48)
  - Obese: TR = 1.24 (95% CI, 1.08-1.42)

Table 3. Adjusted TR estimates for rwTTNT from log-normal AFT models[a]

Variables	TR (95% CI)
Age, years	
<65	1 (reference)
65-74	0.97 (0.84-1.11)
75+	0.92 (0.78-1.08)
Race	
White	1 (reference)
Asian	1.17 (0.81-1.68)
Black or African American	**0.85 (0.74-0.99)**
Other/Unknown	0.86 (0.74-1.00)
Ethnicity	
Not Hispanic or Latino	1 (reference)
Hispanic or Latino	1.14 (0.91-1.42)
Unknown	0.94 (0.81-1.09)
BMI at 1L initiation, kg/m2	1.0 (0.99 - 1.00)
Underweight (<18.5)	0.80 (0.53-1.21)
Normal (18.5-<25)	1 (reference)
Overweight (25 to <30)	**1.27 (1.09-1.48)**
Obese (30+)	**1.24 (1.08-1.42)**
Missing	0.86 (0.47-1.56)
Geographic region	
Northeast	1 (reference)
Midwest	1.05 (0.84-1.30)
South	1.03 (0.86-1.23)
West	0.99 (0.79-1.23)
Unknown	0.80 (0.60-1.08)
Insurance status at 1L initiation	
Commercial health plan	1 (reference)
Commercial health plan – Medicare	1.06 (0.90-1.24)
Medicaid	0.88 (0.65-1.20)
Medicare	0.96 (0.79-1.16)
Other government program	1.04 (0.64-1.70)
Other payer – type unknown	1.06 (0.77-1.45)
Patient assistance program	1.39 (0.77-2.50)
Self-pay	1.23 (0.54-2.81)
Uninsured/insurance not documented	1.21 (1.02-1.43)
SES index	
1 (lowest SES)	1.12 (0.94-1.32)
2	1.11 (0.94-1.30)
3	1.12 (0.96-1.32)
4	1.13 (0.96-1.32)
5 (highest SES)	1 (reference)
Unknown	0.84 (0.67-1.06)
Histology at advanced/recurrent diagnosis	
Endometrioid carcinoma	1 (reference)
Carcinosarcoma/MMT	**0.67 (0.57-0.80)**
Clear cell carcinoma	0.97 (0.74-1.26)
Serous carcinoma	**0.81 (0.71-0.92)**
Endometrial cancer, NOS	**0.77 (0.65-0.92)**
Advanced/recurrent	
Advanced	0.97 (0.86-1.09)
Recurrent	1 (reference)
ECOG at 1L initiation	
0-1	1 (reference)
2-4	**0.55 (0.47-0.65)**
Missing	0.97 (0.86-1.09)
MMR/MSI at any time before 1L initiation	
dMMR and/or MSI-H	1 (reference)
pMMR and/or MSS	**0.80 (0.68-0.95)**
Discordant	0.90 (0.56-1.46)
Other	**0.70 (0.50-0.99)**
Missing	**0.80 (0.68-0.95)**
1L initiated before March 2023	
Yes	1.07 (0.93-1.23)
No	1 (reference)
Practice setting	
Academic	1 (reference)
Community	0.76 (0.57-1.02)
Both	1.12 (0.81-1.56)
CCI	
0	1 (reference)
1	1.17 (0.67-2.04)
2	0.94 (0.80-1.11)
3+	0.88 (0.75-1.04)

[a]TR<1 indicates shorter time to 2L therapy; TR>1 indicates longer time to 2L therapy.

1L: first-line; AFT: accelerated failure time; BMI: body mass index; CCI: Charlson Comorbidity Index; dMMR: deficient mismatch repair; ECOG: Eastern Cooperative Oncology Group performance status; MMR: mismatch repair; MMT: Mixed Mullerian tumor; MSS: microsatellite stable; MSI: microsatellite instability; MSI-H: microsatellite instability-high; NOS: not otherwise specified; pMMR: proficient mismatch repair; rwTTNT: real-world time to next treatment; SES: socioeconomic status; TR: time ratio

Discussion

- Evidence for over 3 decades confirms that Black women experience disproportionately higher burden of EC. They also have nearly double the mortality risk from uterine cancer as White women[3,5]
- Further driving these disparities, Black women are more likely to be diagnosed later in disease progression and with aggressive histologic subtypes, associated with poorer prognosis.[3] The results presented are consistent with this existing evidence, Black women were more frequently diagnosed with serous carcinoma and carcinosarcoma/mixed Müllerian tumors than White women
- Our study found that even after adjusting for sociodemographic and clinical characteristics, Black women transitioned to 2L therapy more quickly than White women (a 15% lower time to 2L). As this analysis included only patients who initiated 1L therapy, these disparities likely reflect factors beyond treatment initiation. Understanding factors that drive this disparity will help us eliminate them
- With 1L treatments being relatively comparable between Black and White women, along with time to 1L treatment initiation, the disparities between these 2 racial groups are being driven by factors beyond those that are treatment-related
- Racial disparities in rwTTNT persisted in EC: Black women initiated 2L sooner, indicating faster progression following 1L, despite controlling for a variety of known risk factors. Addressing underlying causes can help improve risk stratification, guide equitable treatment, and reduce disparities among women with EC

Limitations

- Causal interpretations are limited due to the observational design
- Residual confounding due to unmeasured confounders or interrelated factors could affect the interpretability of results
- Smaller sample sizes for patients with certain characteristics may also limit interpretability
- The database may not have adequate representation of Black women. African Americans' historical mistrust of the medical system may extend to releasing their medical records for research.[9-11] However, evidence is mixed about the extent of underrepresentation of Black populations in registries
- Findings are limited to women who initiated 1L treatment; as a result, disparities arising from barriers to access or receiving treatment were not captured

Conclusions

- Racial disparities in rwTTNT persisted in EC: Black women initiated 2L sooner, indicating faster progression following 1L, despite controlling for known risk factors
- Addressing underlying causes can help improve risk stratification, guide equitable treatment, and reduce disparities among women with endometrial cancer

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Disclosures

- Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA
- VT was a contractor working under contract with Atlas on behalf of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, at the time the study was conducted
- HZ was an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA at the time the study was conducted
- KMM, VSP, SM, KM, KW, RM are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA
- AKG has received consulting fees from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; has served as a consultant or advisory and received funding grants from Menarini Stemline Italia SrL, and has received funding grants from Aadi Biosciences and the American Society of Clinical Oncology
- VM has received travel support from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, AstraZeneca, and Karyopharm; is an unpaid consultant for Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Antares Therapeutics, Clovis Oncology, Cullinan Oncology, DualityBio, Eisai, Faeth Therapeutics, GlaxoSmithKline, Genmab, Immunocore, iTeos Therapeutics, Karyopharm Therapeutics, Jazz Pharmaceuticals, Eli Lilly, Mereo BioPharma, MorphoSys, MSD (UK) Limited, London, UK, Novartis, Ottimo, Regeneron, Scorpion Therapeutics, Stemline Therapeutics, Sutro Biopharma, and Zymeworks; and has received institutional grants or contracts from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, AstraZeneca, Bristol Myers Squibb, Cullinan Oncology, DualityBio, Eisai, Faeth Therapeutics, Jazz, Karyopharm Therapeutics, Takeda, and Zymeworks.

Presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); May 17-20, 2026; Philadelphia, PA, USA.