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Clinical Cancer Research

Insurance Clearance for Early-Phase Oncology Clinical Trials Following the Affordable Care Act

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Abstract

Purpose: The Affordable Care Act (ACA) required that private insurance plans allow clinical trial participation and cover standard-of-care costs, but the impact of this provision has not been well-characterized. We assessed rates of insurance clearance for trial participation within our large early-phase clinical trials program, before and after implementation of the requirement.

Experimental Design: We analyzed the departmental database for the Clinical Center for Targeted Therapy (CCTT) at MD Anderson Cancer Center (Houston, TX). Among patients referred for sponsored trials, we described rates of insurance clearance and prolonged time to clearance (at least 14 days) from July 2012 to June 2013 (baseline), July 2013–December 2013 (following CCTT staffing changes in July 2103), and January 2014–June 2015 (following implementation of the ACA). We used multivariable logistic regression models to compare rates across these time periods.

Results: We identified 2,404 referrals for insurance clearance. Among privately insured patients, insurance clearance rates were higher for those referred from January 2014 to June 2015 than for those referred from July 2012 to June 2013 (OR, 4.72; 95% CI, 2.96–7.51). There was no association between referral period and clearance rates for Medicare/Medicaid patients ($P = 0.25$). Referral from January 2014 to June 2015 was associated with lower rates of prolonged clearance among both privately insured (OR 0.57; 95% CI, 0.38–0.86) and Medicare/Medicaid patients (OR 0.39; 95% CI, 0.19–0.83).

Conclusion: Within our large early-phase clinical trials program, insurance clearance rates among privately insured patients improved following implementation of the ACA's requirement for coverage of standard-of-care costs. *Clin Cancer Res; 23(15); 1–8.* *©2017 AACR.*

Introduction

Historically, less than 5% of patients with cancer in the United States have enrolled in clinical trials (1–4). Older patients, racial and ethnic minorities, and patients with lower incomes are less likely to discuss the option of participating in a trial and to enroll in one (4–6). However, clinical trials are essential to the development of new treatments for cancer, and phase I studies in particular have become increasingly important as the number of candidate targeted therapies and immunotherapies under study has increased (7).

In addition to the cost of a new therapy under consideration within the context of a clinical trial, participants may incur additional costs, related to care such as required office visits, imaging, or laboratory work. Nevertheless, prior studies have demonstrated that the total cost of treating a patient on a clinical trial may be, at most, modestly higher than that of treating a patient off of a trial protocol (8, 9). Since 2000, Medicare has explicitly covered the routine costs of clinical trials with therapeutic intent (10). By 2003, 19 states had passed laws mandating that private insurance plans provide coverage for routine medical care for patients participating in cancer clinical trials (11). As of 2006, 20 states had such laws, and insurers in three more states had agreed to voluntarily cover costs associated with clinical trials (12). Texas passed such a law in 2009 (13, 14).

The Patient Protection and Affordable Care Act (ACA) of 2010 was the first federal law to mandate that group health plans and state-licensed insurance issuers provide coverage of standard-of-care medical costs for patients enrolled in approved clinical trials, effective January 1, 2014. In this context, "approved" trials are those approved or funded by the NCI, CDC, CMS, Department of Defense/VA, cooperative group or center affiliated with those entities, or the Department of Energy, and must be conducted under an investigational new drug application or be exempt from such an application (15). Nevertheless, several factors mitigate the potential impact of the law. For example, patients may effectively be excluded from clinical trial coverage if their care networks do not include an institution conducting a trial, and such terms as "standard of care costs" eligible for coverage remain vague (16). In addition, the ACA requirement for coverage of routine care on clinical

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Before the ACA, legal requirements for coverage of the standard-of-care costs of clinical trials for privately insured patients were heterogeneous and varied by state. The ACA required coverage of these costs for all privately insured patients enrolled in approved clinical trials. We analyzed the experience of our large early-phase clinical trials program with insurance approval for clinical trials before and after the ACA was implemented; we found that approval rates for privately insured patients increased after implementation, but that rates of prolonged clearance trended similarly for both privately insured patients and those with government insurance. These results will inform assessment of the impact of the ACA on cancer research.

trials excluded "grandfathered" plans in existence before March 23, 2010, unless those plans subsequently reduced benefits or increased premiums (17). Furthermore, the ACA requirement did not extend to state Medicaid plans (18), and Medicaid coverage for routine care costs in cancer clinical trials is required only in some states; Texas is among those states that now has such a requirement (13, 17). Finally, recent political shifts have called the future of the ACA itself into question.

Despite this changing legal landscape, the impact of insurance denials on patient enrollment in clinical trials has not been well characterized. One study of patients with cancer who consented to clinical trials from 2003 to 2008 at a large comprehensive cancer center found that 13.6% of patients were denied coverage for clinical trial participation. None of those patients were then treated on a therapeutic trial (19).

Our specific aim in this analysis was to describe our program's experience with insurance clearance for clinical trial enrollment, and rates of prolonged time to insurance clearance, before and after implementation of the ACA's requirement for coverage of standard-of-care costs. We assessed patients evaluated by the early-phase clinical trials program at the University of Texas MD Anderson Cancer Center from July 2012 to June 2015.

Materials and Methods

Study design

The MD Anderson Department of Investigational Cancer Therapeutics (ICT), and its associated clinic, the Clinical Center for Targeted Therapy (CCTT), were established in 2004. The purpose of the unit is to conduct novel phase I and phase II oncology clinical trials in a centralized unit within MD Anderson Cancer Center (Houston, TX). In 2015, the CCTT evaluated over 3,000 patients and enrolled nearly 1,500 patients on over 150 active oncology clinical trials.

We identified patients evaluated by the CCTT from July 2012 through June 2015 and deemed clinically eligible for participation in a clinical trial. The CCTT maintains a database of all such patients and tracks rates of successful insurance clearance, time to clearance, and whether the clinical trial includes drug(s) provided by a pharmaceutical company. To focus on cases in which only fully standard-of-care costs would have been submitted to patients' insurance and prevent confounding related to shifts in our clinical trials portfolio over time, we restricted the analysis to patients being considered for sponsored trials, defined as those in which an investigational agent would have been provided free of charge. Patients who were considered for more than one clinical trial at different time points were included in the database more than once. We linked these data to the MD Anderson tumor registry for additional information on patient demographics and to the institutional clinical database for information on insurance coverage at the time of referral to the CCTT.

Participants

Patients were included if they were residents of one of the 50 states in the United States or the District of Columbia, had entries in the CCTT database that could be linked to insurance and cancer registry information, were diagnosed with only one primary tumor according to the registry, and had commercial insurance, Medicare, or Medicaid. International, self-pay, and charity care patients were therefore excluded. Patients were also excluded if they did not have clear documentation of insurance clearance status within the CCTT database (Fig. 1). This study was conducted in accordance with the Declaration of Helsinki; it was approved by the Institutional Review Board at MD Anderson Cancer Center (Houston, TX), and the requirement for informed consent in this retrospective analysis was waived.

Outcome variables

Our primary outcomes were (i) the rate of insurance clearance for clinical trial participation and (ii) prolonged time (greater than or equal to 14 days) to clearance among referrals that were cleared. Both were treated as binary variables. For referrals in which there was clear documentation of insurance clearance status but not time to clearance, cases were included in analyses of the former but not the latter outcome.

Independent variables

Our principal independent variables of interest were type of insurance (private insurance only, or any Medicare/Medicaid coverage) and month of referral. Month of referral was divided into three categories (July 2012–June 2013, July 2013–December 2013, and January 2014–June 2015), because staffing changes within the CCTT in July 2013 led to increased prescreening of patients for clinical trial coverage before they were ever considered for a clinical appointment, and the ACA's requirement for coverage of the standard-of-care costs of clinical trials participation took effect in January 2014. We also measured the demographic characteristics of the cohort, including age, gender, race/ethnicity, and marital status, and residency in Texas. We tested an additional independent variable representing whether patients resided in states with clinical trials coverage requirements enacted before the ACA, specifically in the context of phase I trials (12, 14).

Statistical analysis

Statistical analyses were performed using SAS software, version 9.4. Unadjusted analyses were performed using Fisher exact test; when multiple levels of a categorical variable were present, a Monte Carlo simulation of the Fisher exact test (100,000 repetitions) was used. Proportions of referrals with insurance clearance or prolonged time to clearance were represented graphically with 95% exact binomial confidence

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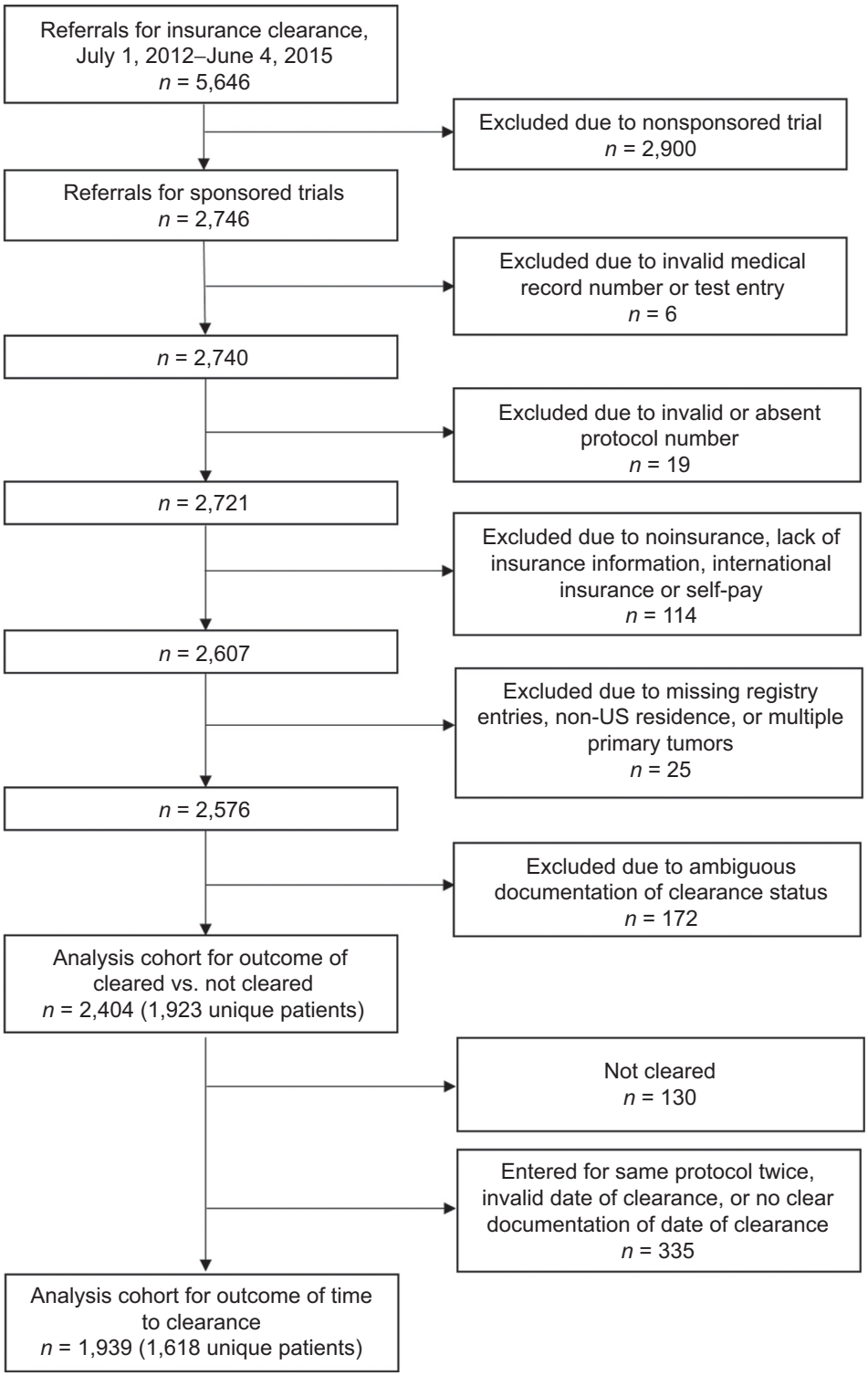

Figure 1.
Derivation of study cohort.

intervals. Primary analyses were performed using multivariable logistic regression models. As individual patients could be referred for insurance clearance and therefore entered in the CCTT database for more than one clinical trial, we also performed sensitivity analyses using generalized linear mixed effects models to account for repeated measures among patients; results were very similar, and we present only the ordinary logistic regression models here. We performed a second sensitivity analysis including only the first referral for each patient; results were again similar, and are presented in Supplementary Table S1. Nominal two-tailed P values <0.05 were considered statistically significant.

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Table 1. Unadjusted rates of insurance clearance for clinical trials

	Total *N* (%) 2,404 (100)	Cleared (%) 95	*P*[a]
Age			
<20	32 (1)	94	0.005
20–29	70 (3)	94	
30–39	158 (7)	96	
40–49	364 (15)	91	
50–59	693 (29)	94	
60–69	745 (31)	95	
70–79	315 (13)	98	
>79	27 (1)	96	
Gender			
Male	1,102 (46)	94	0.47
Female	1,302 (54)	95	
Race/ethnicity			
White	1,771 (74)	95	0.37
African American	197 (8)	94	
Hispanic	265 (11)	95	
Other	171 (7)	92	
Marital status			
Divorced/separated	183 (8)	92	0.29
Married	1,769 (74)	95	
Single	357 (15)	94	
Widowed	78 (3)	99	
Unknown	17 (1)	100	
Resident of Texas			
No	952 (40)	93	0.01
Yes	1,452 (60)	96	
Insurance			
Private only	1,430 (59)	93	<0.001
Any Medicare/Medicaid	974 (41)	97	
Time period referred			
July 2012–June 2013	570 (24)	90	<0.001
July 2013–December 2013	344 (14)	95	
January 2014–June 2015	1,490 (62)	96	

[a]Calculated using the Fisher exact test.

Results

Study cohort

The demographics of our study cohort are detailed in Table 1. The ACA requirement for insurance coverage of the standard-of-care costs of clinical trial participation took effect in January 2014; within our cohort of 2404 referrals, 24% occurred between July 2012 and June 2013, 14% occurred between July 2013 and December 2013, and 62% occurred between January 2014 and June 2015. Sixty percent corresponded to residents of Texas. An additional 8% of referrals corresponded to patients residing in other states with pre-existing requirements for coverage of phase I clinical trial costs before the ACA.

Rates of clearance and prolonged time to clearance

Overall, insurance clearance for clinical trial participation was accomplished for 95% of referrals. The clearance rates ranged from 85% among privately insured patients referred from July 2012 to June 2013, to 99% among patients with government insurance referred from July 2013 to December 2013 (Fig. 2). Among cleared referrals, the median time to clearance was 3 days, and the rate of prolonged time to clearance (14 days or greater) was 10.5%; the rates of prolonged time to clearance ranged from 3% among Medicare/Medicaid patients from January 2014 to June 2015, to 25% for privately insured patients in July 2013–December 2013 (Fig. 3).

In unadjusted analyses, there was statistically significant variation in the probability of insurance clearance according to age ($P = 0.006$), type of insurance ($P < 0.001$), time period ($P < 0.001$), and residency in Texas ($P = 0.01$), although the extent of the variation was small (range within each of these

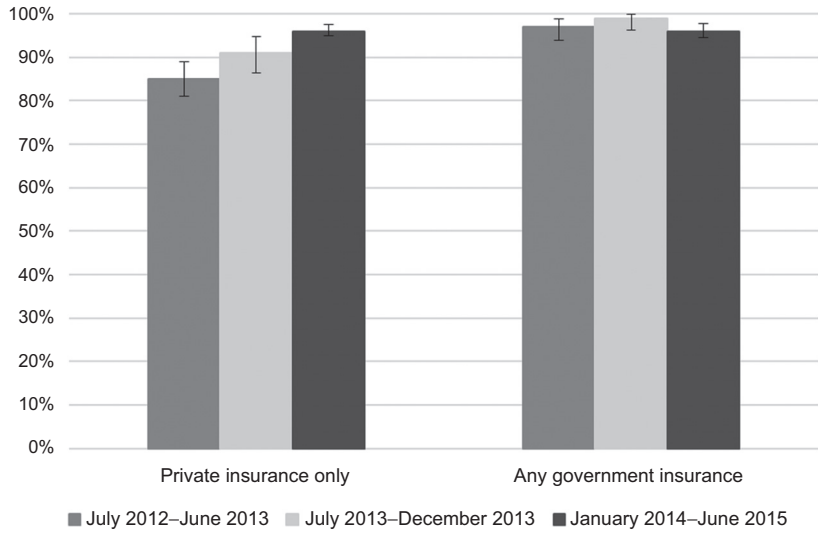

Figure 2.
Rates of insurance clearance by time period and insurance type[a]

	July 2012–June 2013 *N*	July 2013–December 2013 *N*	January 2014–June 2015 *N*
Private insurance only	339	202	889
Any government insurance	231	142	601

[a]Error bars represent 95% exact binomial confidence intervals.

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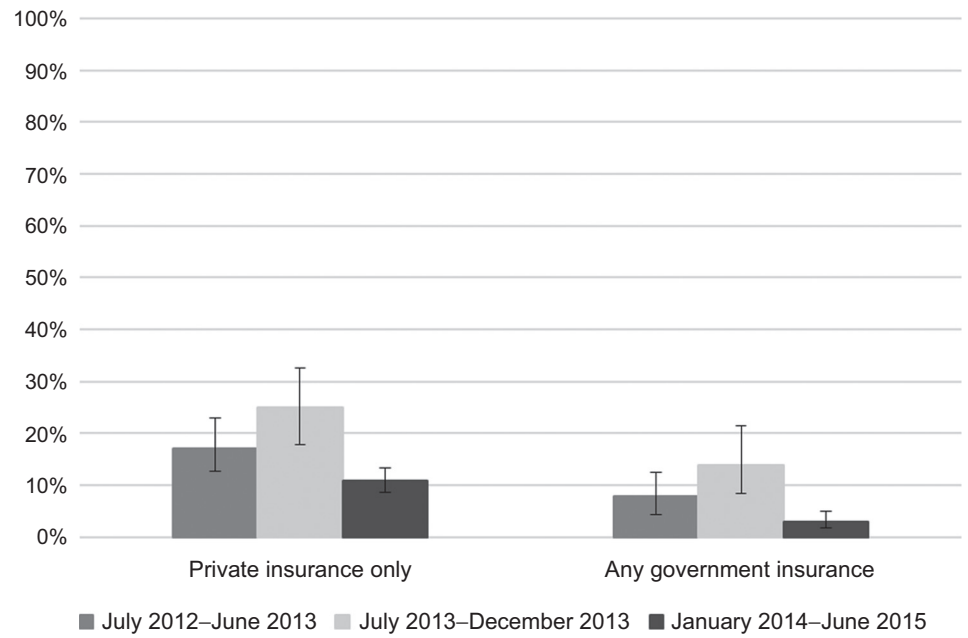

Figure 3.

Prolonged time to insurance clearance by time period and insurance type[a]

	July 2012–June 2013	July 2013–December 2013	January 2014–June 2015
	N	*N*	*N*
Private insurance only	235	142	744
Any government insurance	182	121	515

[a]Error bars represent 95% exact binomial confidence intervals.

groups, 90%–98%). Among the 40% of referrals corresponding to patients residing in states other than Texas, there was no significant variation in the probability of insurance clearance according to whether those states had requirements for clinical trials coverage before the ACA ($P = 1.0$). There was no association between insurance clearance and gender, race/ethnicity, or marital status (Table 1).

Similarly, there was variation in the outcome of prolonged time to clearance according to age ($P < 0.001$), insurance type ($P < 0.001$), time period ($P < 0.001$), and residency in Texas (0.004), but not according to gender, race/ethnicity, or marital status. Among non-Texas residents, there was no association between prolonged time to clearance and residency in a state with a pre-ACA clinical trials coverage requirement ($P = 0.49$; Table 2).

Rate of clearance: multivariable models. In an initial multivariable model, age was not statistically significantly associated with clearance ($P = 0.29$) after adjustment for insurance type; therefore, age was not included in subsequent models. In another preliminary multivariable logistic regression model assessing the rate of insurance clearance, there was a statistically significant interaction between time period and private insurance coverage ($P < 0.001$), indicating that the association between time period and insurance clearance was different for privately insured patients than for patients with any Medicare or Medicaid coverage. There was no interaction between private insurance coverage and residency in Texas ($P = 0.60$), or between time period and residency in Texas ($P = 0.86$). Therefore, we ran subsequent models separately for privately insured patients versus patients with any Medicare or Medicaid coverage, and included, as independent variables, time period and residency in Texas.

Among privately insured patients, those referred for clearance from January 2014 to June 2015 were more likely to be cleared than those referred from July 2012 to June 2013 [OR, 4.72; 95% confidence interval (CI), 2.96–7.51; $P < 0.001$]. Those referred from July 2013 to December 2013 were also more likely to be cleared than those referred from July 2012 to June 2013 (OR, 1.92; 95% CI, 1.08–3.41; $P = 0.03$; Table 3). Patients residing outside of Texas were less likely to be cleared (OR, 0.58; 95% CI, 0.38–0.88; $P = 0.01$; Table 3).

Among patients with any Medicare or Medicaid coverage, there was no significant association between referral time period and insurance clearance rate ($P = 0.25$ for the combined hypothesis test across all three levels of the time period variable). There was also no association between residency in Texas and the probability of clearance ($P = 0.46$ for patients with government insurance; Table 3).

Prolonged time to clearance: multivariable models. Among referrals with successful insurance clearance, age was again not associated with prolonged time to clearance ($P = 0.32$) after adjustment for insurance type, so it was not included in subsequent models. For this outcome, there was no interaction between period of referral and either type of insurance coverage ($P = 0.28$) or residency in Texas ($P = 0.08$) with respect to the outcome of prolonged time to clearance. However, to facilitate interpretation of the data and

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Table 2. Unadjusted rates of prolonged time to insurance clearance for clinical trials

	Total *N* (%) 1,939 (100)	Prolonged (%) 11	*P*[a]
Age			
<20	27 (1)	7	<0.001
20–29	58 (3)	14	
30–39	126 (7)	13	
40–49	269 (14)	10	
50–59	558 (29)	14	
60–69	617 (32)	10	
70–79	260 (13)	4	
>79	24 (1)	0	
Gender			
Male	893 (46)	11	1.0
Female	1,046 (54)	11	
Race/ethnicity			
White	1,431 (74)	10	0.75
African American	161 (8)	10	
Hispanic	213 (11)	13	
Other	134 (7)	10	
Marital status			
Divorced/separated	136 (7)	10	0.33
Married	1,428 (74)	11	
Single	295 (15)	12	
Widowed	66 (3)	5	
Unknown	14 (1)	0	
Resident of Texas			
No	746 (38)	13	0.004
Yes	1,193 (62)	9	
Insurance			
Private only	1,121 (58)	14	<0.001
Any Medicare/Medicaid	818 (42)	6	
Time period referred			
July 2012–June 2013	417 (22)	13	<0.001
July 2013–December 2013	263 (14)	20	
January 2014–June 2015	1,259 (65)	8	

[a]Calculated using the Fisher exact test.

comparison with the analyses of rates of clearance, we again ran separate models for privately insured patients and those with any government insurance.

Among privately insured patients, referral during the January 2014–June 2015 time period was associated with a lower rate of prolonged time to clearance than referral from July 2012 to June 2013 (OR, 0.57; 95% CI, 0.38–0.86; $P = 0.007$). Referral from July 2013 to December 2013 was associated with a slightly higher rate of prolonged time to clearance than referral from July 2012 to June 2013 (OR, 1.49; 95% CI, 0.89–2.49), but this association did not reach statistical significance ($P = 0.13$). There was no association between residency in Texas and prolonged time to clearance ($P = 0.14$; Table 3).

Similarly, among patients with any Medicare/Medicaid coverage, referral from January 2014 to June 2015 was associated with a lower rate of prolonged time to clearance compared to referral from July 2012 to June 2013 (OR, 0.39; 95% CI, 0.19–0.83), but there was no significant association between referral from July 2013 to December 2013 and prolonged time to clearance (OR, 2.00; 95% CI, 0.94–4.25). Residency outside of Texas was associated with a higher probability of prolonged time to clearance (OR, 2.36; 95% CI, 1.29–4.32, $P = 0.006$; Table 3).

Discussion

The ACA's requirement that private health insurance plans cover the standard-of-care costs of clinical trial participation has the potential to increase access to clinical trials for patients with cancer. However, the future of the ACA itself has become an open question, such that assessment of the impact of its various provisions is increasingly important for subsequent policymaking. To assess the early potential impact of the clinical trial coverage requirement, we analyzed the rate of successful insurance clearance for clinical trial participation within the large early-phase clinical trials program at our institution. Overall, the rates of insurance clearance were high throughout our time periods of interest, and the rates of prolonged time to clearance were fairly low. Still, we found that, for privately insured patients, clearance rates were higher during the 18 months following implementation of the ACA's coverage requirement than they were during the reference period ending 6 months before implementation. For patients with Medicare or Medicaid, there was no clear change in successful insurance clearance following the ACA. The rates of prolonged time to insurance clearance were lower following implementation of the ACA in both the privately insured cohort and the Medicare/Medicaid groups than they were in the reference period. Residency in Texas was associated with slightly higher clearance rates and lower prolonged time to clearance, possibly due to some combination of Texas' clinical trials requirement passed in 2009 and smoother logistics in dealing with in-state insurers.

It is therefore possible that the ACA clinical trial coverage requirement may be facilitating insurance clearance for clinical trials participation among privately insured patients at our institution. Many states, including Texas, also enacted clinical trials coverage requirements before the ACA was implemented. However, the ACA contained the first national requirement for clinical trials coverage in private plans, which may have directly affected out-of-state patients seen at our center and introduced a regulatory consistency with the potential to facilitate approval for all patients. It is worth noting that, from a payor's perspective, even in

Table 3. Rates of clearance for trials and prolonged clearance, by time period

			T2 vs. T1		T3 vs. T1		Texas resident (no vs. yes)	
Outcome	**Insurance**	***N***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Clearance	Private only	1430	1.92 (1.08–3.41)	0.03	4.72 (2.96–7.51)	<0.001	0.58 (0.38–0.88)	0.01
Clearance	Any Medicare/Medicaid	974	4.44 (0.54–36.4)	0.17	0.82 (0.34–1.94)	0.65	0.76 (0.36–1.58)	0.46
Prolonged clearance	Private only	1121	1.49 (0.89–2.49)	0.13	0.57 (0.38–0.86)	0.007	1.29 (0.92–1.83)	0.14
Prolonged clearance	Any Medicare/Medicaid	818	2.00 (0.94–4.25)	0.07	0.39 (0.19–0.83)	0.02	2.36 (1.29–4.32)	0.006

NOTE: Results were generated using multivariable logistic regression models. Each row represents one model, for example, one model was fit to data from 1,430 patients with "private only" insurance for clearance analysis. Independent variables were time period (T1, T2, or T3) and residency in Texas (no/yes). Clearance ORs greater than 1 indicate that clearance rates increased in the corresponding column compared with the reference group. Prolonged clearance ORs less than 1 indicate that the proportion of patients with prolonged clearance times (>14 days) was lower in the corresponding column.
Abbreviations: *N*, number of patients; T1 = 7/2012–6/2013, T2 = 7/2013–12/2013, T3 = 1/2014 – 6/2015.

cases where treatment on an individual clinical trial might be more expensive, a trial's ability to determine which treatments are most valuable can also ultimately be useful to insurers as well as to patients.

The major limitation of our single-institution analysis is our inability to fully account for secular trends within the early-phase clinical trial program. A larger study would likely require either a concerted and specific effort among institutions, or collaboration with insurers, who would likely have the most reliable institution-independent information on all requests for coverage of costs associated with clinical trials, whether confirmed or denied. We assessed only referrals for sponsored trials, in which insurers would not be asked to pay for the cost of a trial drug, to prevent confounding related to a simultaneous shift in portfolio over time away from investigator-initiated trials. Still, the administration of the program underwent a leadership change in July 2013, at which time, efforts to streamline operations included increased prescreening of patients for clinical trial coverage prior to an initial clinical evaluation and entry in the database. The ACA's coverage provision took effect in January 2014, such that these data cannot determine whether improvements occurring after January 2014 were due to the ACA or to evolving effects of that earlier leadership change. In addition, the number of employees working on clinical trial insurance clearance increased from six to 10 in September 2013, and we could not adjust for this staffing change, due to its collinearity with the primary time period independent variable. Nevertheless, since the department's clinical volume was also increasing substantially during that time in the context of a shift in focus toward industry-sponsored trials, the ratio of staff to referrals for clearance remained relatively stable.

For the outcome of the rate of insurance clearance for trials, improvements were seen in the privately insured population but not in the population with governmental insurance. This implies a temporal effect specific to the privately insured population, as would be expected of an effect of the ACA's coverage requirement; Medicare already had a clinical trial coverage requirement before the ACA, and the coverage requirement did not extend to Medicaid plans. However, this specific effect was not seen in the outcome of prolonged time to clearance; it remains possible that secular trends within the department specifically improved rates of clearance among the privately insured population, and because the privately insured population had lower clearance rates at the beginning of our assessment period, it had more room to improve, regardless of the mechanism.

In addition, this analysis focused on the issue of clearance for clinical trials among patients whose insurance allowed access to our institution in the first place. Recently, concerns have arisen about the breadth of provider networks available particularly within exchange networks under the ACA, and about the impact of narrow networks on access to high-quality cancer care (20–23). We could not assess the impact of exclusion of our institution from provider networks on the ability of interested patients to enroll in clinical trials in the phase I program. Finally, the ACA's requirement for coverage of clinical trial costs did not extend to "grandfathered" plans that existed before the ACA and have not subsequently changed their premium or benefit structures (17), and we could not assess how often patients had private plans with that status.

In conclusion, within the large early-phase clinical trials program at our institution, we found that rates of successful insurance clearance for clinical trial enrollment among privately insured patients have increased following implementation of the clinical trials coverage requirement for private plans under the ACA. Rates of prolonged time to insurance clearance have decreased following implementation of the requirement, although this change occurred among both privately insured patients and patients with government insurance. If validated in other settings, these results will provide context for subsequent efforts to increase overall clinical trial participation within the context of an evolving health care system.

Disclosure of Potential Conflicts of Interest

R. Kurzrock has ownership interests (including patents) in and reports receiving commercial research grants from CureMatch, Inc., and is a consultant/advisory board member for Actuate Therapeutics and Xbiotech. No potential conflicts of interest were disclosed by the other authors.

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