The Impact of Insurance on Access to Cancer Clinical Trials at a Comprehensive Cancer Center

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Abstract

Purpose: Cancer patients at Johns Hopkins undergo insurance clearance to verify coverage for enrollment to interventional clinical trials. We sought to explore the impact of insurance clearance on disparities in access to cancer clinical trials at this urban comprehensive cancer center.

Experimental Design: We evaluated the frequency of insurance-based denial of access to cancer clinical trials over a 5-year period after initiation of a formal insurance clearance process. We used a case-control design to compare demographic and clinical parameters of patients denied or approved for clinical trials participation by their insurance company in a 3-year interval.

Results: From July 2003 to July 2008, insurance requests for clinical trial participation were submitted on 4,617 consented cancer patients at Johns Hopkins. A total of 628 patients (13.6%) with health insurance were denied therapeutic trial enrollment owing to lack of insurance coverage for participation. A total of 254 patients denied enrollment from 2005 to 2007 were selected for further analysis. Two-hundred sixty randomly selected patients approved for clinical trial participation served as controls. Patients approved were on average older (59.2 versus 54.9 years) than patients denied (P = 0.0001). Residents of Pennsylvania, which lacks a state law mandating cancer clinical trial coverage for residents, were overrepresented among the denied patients (P = 0.0009). No statistically significant variance in the likelihood of insurance denial was found on the basis of sex, race, stage of disease, or presence of comorbidities.

Conclusions: Denial of access to therapeutic clinical trials, even among insured patients, is a significant barrier to clinical cancer research. This barrier spans racial, ethnic, and gender categories. Clin Cancer Res; 16(24); 5997–6003. ©2010 AACR.

Health insurance reform has again become an epicenter of political debate in the United States. Congress, the President, and the media have raised awareness of insurance company practices, such as coverage denials based on preexisting conditions, which can limit access to care. The recent health care reform debate did not focus significant attention on the impact of reform measures on investigational clinical trials that are the cornerstone of improving cancer care. Nonetheless, the Patient Protection and Affordable Care Act enacted March 23, 2010 included a requirement that health plans and insurance issuers provide coverage for routine care costs associated with participation in a clinical trial. This requirement is slated to take effect in 2014.

Since President Nixon declared a “war on cancer,” disparities between cancer incidence and outcome for minority populations have persisted, and in some cases have increased (1). Differences in quality and access to cancer screening, early detection, and treatment have been described as factors contributing to this variance (2–5). As larger numbers of uninsured Americans receive health insurance as a result of the new law, access to basic cancer services (such as prevention, screening, and treatment programs) may improve.

More than 1.4 million Americans were diagnosed with cancer in 2008, resulting in more than 560,000 deaths (6). Only a small fraction of adult cancer patients participate in therapeutic clinical trials, the foundation for development of new knowledge in the prevention, detection, and treatment of malignant diseases. Accrual of certain underrepresented populations is particularly low, including: African-American men; Latinos and/or Hispanics; Asian and Pacific Islanders; American Indians and/or Alaska Natives; older adults (age > 65 years); residents of rural communities; and individuals with low socioeconomic status (7, 8). Many barriers to clinical trial participation by these groups have been identified, including but not limited to lack of access to care, mistrust...
of research, logistical and financial challenges associated with traveling to cancer centers, and the definition of study entry requirements (7, 9). Issues of equity and affordability of care are further discussed in the accompanying article by Schnipper and colleagues (10).

In addition to demographic factors, lack of health insurance is a barrier that restricts access to cancer care and clinical trial participation in the United States (11). Even for patients with insurance coverage, the costs of routine care associated with trial participation may be specifically excluded from insurance policy coverage. Many cancer centers, including ours, have begun to seek authorization from insurance carriers and health plans prior to enrolling patients in therapeutic trials. Patients who lack coverage of clinical trial costs may be financially unable to participate in studies for which they would otherwise be eligible. The preauthorization process was considered necessary, in part, because the potential for denial of coverage meant that patients were not aware of all potential costs associated with trial participation prior to enrolling. At best, the need to obtain clarity about clinical trials coverage delays trial enrollment. At worst, the denial of coverage can restrict a patient's participation by making it financially unfeasible.

Unlike most private payers, the Medicare program has a clear policy of covering clinical trials. In 2000, President Clinton signed an executive memorandum directing the Center for Medicare & Medicaid Services to authorize payment for routine care costs associated with clinical trial participation. This National Coverage Decision was followed by a 14% increase in accrual to National Cancer Institute (NCI)–sponsored cancer clinical trials among Medicare participants (12). Insurance coverage and geographic location remain influential factors in many patients’ decision to participate in clinical trials (13, 14). Marked variation exists in state laws governing private insurance companies and their coverage decisions. Twenty-nine states and the District of Columbia presently require insurance companies to cover patient care costs in cancer clinical trials (Fig. 1). An additional five states have negotiated agreements with insurance companies to voluntarily cover the costs of clinical trials. However, state laws do not impact health plans regulated under the federal Employee Retirement Income Security Act (ERISA). The Patient Protection and Affordable Care Act sets a federal minimum requirement for coverage of clinical trials, applying to both federally regulated health plans and state-regulated health insurance issuers, as well as the Federal Employees Health Benefits Program. The requirement takes effect on January 1, 2014. Various other implications of this national health care reform act are discussed in greater detail in the accompanying article by Dalton and colleagues (15).

We sought to determine the prevalence of exclusion from clinical trials as a result of insurance denials. Because of the known association between minority status and the likelihood of being underinsured, we hypothesized that these denials might, in particular, limit enrollment of underrepresented minorities in clinical trials at our cancer center. The main goals of this study were to measure the impact of insurance coverage on accrual and to explore the current patterns of accrual of underserved populations to cancer clinical trials at an urban NCI-designated comprehensive cancer center.

**Patients and Methods**

The Johns Hopkins University Hospital established an internal agency, Access Services, to confirm insurance coverage for investigational clinical trials. Beginning in 2003, patients consented for therapeutic cancer clinical trials at the Sidney Kimmel Comprehensive Cancer Center (SKCCC) were required to receive insurance coverage clearance prior to enrollment. After obtaining Institutional Review Board approval for these analyses, we reviewed the demographic and clinical data of both a cohort of patients denied clinical trial coverage and a cohort of patients approved for clinical trial coverage over a 3-year period (2005 to 2007).

All denied patients in the 3-year interval were included in the analysis. A computerized randomization program was used to select a cohort of approved patients to serve as controls. The insurance clearance database contains each patient’s medical record number, insurance company name and plan, number of days for a coverage decision by each company, the clinical trial for which each patient was considered, and the ultimate coverage decision for each patient.

Using the patient’s medical record number, a retrospective chart review was done to identify the following for each patient: age, sex, race, insurance company and/or plan, and length of time for the coverage decision. Clinical factors such as cancer diagnosis, stage of disease, Eastern Cooperative Oncology Group (ECOG) performance status, and comorbid health conditions were also collected.

Data were analyzed with SAS software version 9.1 (SAS Institute). Descriptive statistics were used to summarize patients’ medical and insurance information. Means, standard deviations, and 95% CIs were used to report continuous data, and percentages used to report categorical data. Means were compared using Student's t tests, and proportions using \( \chi^2 \) statistics. All \( P \)-values are two sided.

**Results**

From July 2003 to July 2008, 4,617 patients signed informed consent documents to enroll in cancer treatment trials at the SKCCC and were referred for insurance coverage clearance. Six-hundred twenty-eight patients (13.6%) were denied coverage. Of those denied, a total of 490 patients (78%) had insurance policies that generally allowed coverage for clinical trial participation. However, they were denied coverage because of issues particular to the trial being considered, for example, phase of the trial. The remaining 138 patients (22%) were denied because their insurance policies lacked any clinical trial benefit. None of the patients who were denied insurance coverage for participation were treated on therapeutic clinical studies.
There was marked variability in the approval rate for clinical trial participation among the insurance providers. Table 1 summarizes the rates of approval among insurance carriers and health plans reviewing at least 70 requests for participation from SKCCC between July 2003 and July 2008. Not shown in Table 1 is the variability in rates of approval by individual carriers and plans over time. For example, after meetings between representatives of Johns Hopkins Medicine and Federal BlueCross/BlueShield, their rate of approval has increased to 100% of requests in the current fiscal year.

We have tracked clinical trial accrual by underrepresented minority patients over time in the cancer center. Total annual participation in interventional cancer clinical trials at SKCCC increased from 860 patients in 2004 to 1,078 patients in 2008. The total number of patients seen at SKCCC (analytic cancer cases) showed a similar increase, from 5,493 patients in 2004 to 6,283 patients in 2008. As shown in Fig. 2, the percentage of patients seen who are minorities (non-White) has been relatively stable at between 20.9 and 22.2% from 2005 to 2008. Minority participation in interventional cancer clinical trials has increased each year, with some suggestion that the gap between the percent of minority patients seen and the percent of minority patients accrued to studies may be closing over time: the disparity of 4.9% in 2006 has decreased to 1.4% in 2008 (Fig. 2). The disparity in minority accrual to interventional cancer trials at Johns Hopkins was relatively stable at 3.5 to 4.9% over the years 2005 to 2007.

To evaluate demographic and clinical factors associated with insurance denial in greater detail, the cohort of patients from 2005 to 2007 was considered for further analysis. Over this 3-year period, a total of 400 consented patients were initially denied coverage. Following a denial by the insurance carrier or health plan, an appeals process was initiated for most patients by the research nurse and clinician investigator; after appeal and further review, an additional 146 patients were approved for coverage of a cancer treatment trial. The 254 remaining patients were denied coverage after appeal and comprise the cohort of denied patients in which detailed chart reviews were conducted. A total of 260 insurance-approved patients who participated in cancer treatment trials were randomly selected as controls.

The mean age of denied patients was 54.9 (95% CI, 53.6-56.2), and the mean age of approved patients was 59.2 (95% CI, 57.8-60.5; Table 2). This difference is statistically significant ($P = 0.0001$), consistent with an effect of Medicare provision of clinical trial coverage for seniors. There was no difference in gender between denied and approved patients, with 42% of each group being women. There were also no statistically significant differences by race between the denied and approved groups. More than 80% of each cohort was White, and 12 to 13% of patients in each group were African-American and/or Black, with the remainder representing other races, primarily Asian. Only a small percentage (approximately 2%) of patients seen at Johns Hopkins is Hispanic, precluding any analysis of differential enrollment by ethnicity.
The denied and approved cohorts displayed differences by disease type. Among those patients denied enrollment, the most prevalent diseases included prostate (17.7%), lung (11.4%), colon (11.0%), and pancreas cancers (11.0%). Among those approved, the most prevalent diseases included prostate (16.9%), breast (15.8%), and pancreas cancers (13.5%).

The majority of patients in each group considered for trial enrollment had advanced stage disease (stage III-IV or recurrent disease): 196 (77%) of the denied patients and 173 (66%) of the approved patients. The ECOG performance status of the groups revealed no statistically significant differences, with the majority of patients presenting with performance status 0 or 1. A small minority of patients in each cohort showed two or more comorbid illnesses, with no statistical differences noted between groups. The most common comorbid illnesses identified for each cohort were hypertension and dyslipidemia.

There was no observed statistically significant distinction between the two groups with respect to the type of treatment protocol for which they had consented (Fig. 3). Of the approved patients, 83% were accrued to a phase I, II, or combined phase I-II trial. Of the denied patients, 85% were denied coverage of a phase I, II, or combined trial.

The average number of days for an initial coverage decision was 5.98 business days (95% CI, 5.28–6.67) for the denied patients and 5.51 business days (95% CI, Table 1. Rates of insurance company approval for enrollment in cancer center clinical trials at Johns Hopkins (July 2003 to July 2008)

<table>
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<tr>
<th>Insurance Provider*</th>
<th>Cases Reviewed (N)</th>
<th>Percent Final Approval</th>
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<tr>
<td></td>
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<td></td>
<td>Average</td>
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<tr>
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<td>BC/BS Federal</td>
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<td>46</td>
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*Only companies reviewing more than 70 cases are listed; approval rates for some carriers have changed over time. Abbreviations: EHP, Employer Health Programs; BC/BS, BlueCross/BlueShield; DC, District of Columbia; NASCO, National Account Service Company; PPO, preferred provider organization; UHC, United Healthcare.

Fig. 2. Total minority patients treated, and minority patients enrolled onto interventional clinical trials. The blue curve indicates the total percentage of non-White analytic cancer cases, residents of the SKCCC catchment area, treated by year in the cancer center. The red curve indicates the percentage of non-White patients enrolled onto interventional cancer clinical trials, by year at SKCCC. The disparity between the curves had ranged from 4.9 to 3.5% in the years 2005 to 2007, but narrowed in 2008 to 1.4%.

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There were also no significant differences in the mean number of days for coverage decision by racial group. Most patients (81.3%) considered for trial accrual at Johns Hopkins were residents of Maryland (53.5%), Pennsylvania (16.7%), and Virginia (11.0%). Residents of Pennsylvania were significantly overrepresented in the denied cohort (22.6% of the denied versus 11.2% of the approved; \( P = 0.0009 \)); in contrast Maryland and Virginia residents comprised 51.2% and 10.1% of denied and 55.8% and 11.9% of the approved cohorts, respectively (Fig. 4). Pennsylvania, unlike Maryland and Virginia, has no state law requiring insurance companies to cover patient care costs associated with clinical trials. Despite state laws, some Maryland and Virginia residents are denied clinical trial coverage by insurance carriers located out of state, or by federally regulated plans.

### Discussion

Cancer patient outcomes among participants in randomized clinical research protocols receiving an investigational therapy are, on average, as good or better than those of patients receiving a standard therapy (16). Even the earliest phase of clinical research, phase I studies, have an overall response rate of approximately 10% for adult solid tumor patients (17). Groups including the American Society of Clinical Oncology and the National Comprehensive Cancer Network assert that clinical trials are a vital component of quality cancer care. Clinical trials participation is also necessary to discover more effective treatments for cancers. Patient barriers to clinical research, particularly therapeutic cancer clinical trials, need to be minimized.

Review of our institutional insurance clearance process documents that coverage of clinical trials poses a challenge to many patients willing to enroll in a trial. Denial of coverage is a practice that spans major demographic categories and types of trials. Additionally, denial of coverage is more significant in the state of Pennsylvania, which lacks a state law to require insurers to provide coverage. We found no evidence that the insurance clearance process introduced biases in enrollment by race, gender, or comorbidity.

This analysis of insurance clearance can be placed in the context of the several other documented barriers to clinical trials accrual. In this study, we were interested in isolating the impact of insurance review per se, something that had not been addressed in prior analyses. Patients included in this data set had cleared many other possible barriers to accrual. They are individuals who (a) came to a comprehensive cancer center for evaluation and care, (b) had health insurance, (c) were offered a clinical trial, (d) met study eligibility criteria, and (e) were able and willing to provide written informed consent. Our analysis did not attempt to redemonstrate the influence of these other barriers to clinical trial participation or their differential impact on underrepresented minority populations.

Imposition of an insurance clearance process necessarily delays initiation of therapy, on average by approximately a week in our center, and for one insurance carrier, over 2 weeks. Our retrospective review of patients referred for insurance clearance does not assess the number of patients who chose to pursue off-protocol therapy rather than clinical trial enrollment because of this inherent delay.

More than 20% of patients denied coverage of trial participation had insurance plans that specifically lacked a clinical trial benefit. In states where private insurance companies are required to cover routine costs of care for...
patients on therapeutic clinical trials, coverage seemed to be enhanced, but no published studies specifically measure this impact. Coverage for services mandated on the state level is at best a partial solution, because it does not address ERISA plans and may not cover individuals seeking care across state lines. State residents enrolled in a health plan regulated by federal law (ERISA), or based in a state without mandated coverage, may not in fact have coverage for these “mandated” services. The new federal law will address these gaps beginning in January 1, 2014. The law requires coverage for ERISA plans and standardizes coverage for state-regulated insurance issuers and those covered through the Federal Employees Health Benefits Program.

Of the 400 patients initially denied coverage for clinical research protocols by insurance providers, 146 patients were ultimately enrolled after their original coverage determination was reversed on appeal to the insurer or health plan by our research staff and/or the patient directly. Submission and evaluation of such appeals is complex and time consuming for academic centers and for insurance providers, and is exceedingly stressful for patients.

It is notable that coverage of routine patient care costs does not require insurers to pay for research costs, but only for continued standard-of-care services in conjunction with clinical research. These are costs that would be submitted to the insurance provider whether the patient were treated off protocol or as part of a clinical trial. Several studies have concluded that the difference in costs between routine costs of cancer clinical trials and costs for those treated off protocol is negligible (18–20).

We propose that prospective studies be considered to evaluate the impact of insurance clearance more broadly, across multiple cancer treatment facilities. Such studies could survey the impact of insurance on access to cancer clinical trials at multiple centers, and collectively throughout the nation. These data could have significant health policy implications.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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