Effect of a Clinical Evidence Technology on Patient Skin Disease Outcomes in Primary Care: A Cluster-Randomized Controlled Trial

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ABSTRACT

Objective: Providers’ use of clinical evidence technologies (CETs) improves their diagnosis and treatment decisions. Despite these benefits, few studies have evaluated the impact of CETs on patient outcomes. Investigators evaluated the effect of one CET, VisualDx, on skin problem outcomes in primary care.

Methods: The cluster-randomized controlled pragmatic trial was set in outpatient clinics at an academic medical center in the Northeast. Participants were Primary Care Providers (PCPs) and adult patients seen for skin problems. The intervention was VisualDx as used by PCPs. Outcomes were patient-reported time from index clinic visit to problem resolution, and the number of follow-up visits to any provider for the same problem. PCPs assigned to intervention agreed to use VisualDx as their primary evidence source for skin problems. Control group PCPs agreed not to use VisualDx. Investigators collected outcome data from patients by phone at 30
day intervals. Cox proportional hazards models assessed time to resolution. Wilcoxon-rank sum tests and logistic regression compared return appointments.

**Results:** Thirty-two PCPs and 433 patients participated. In proportional hazards modelling adjusted for provider clusters, the days from index visit to skin problem resolution were similar in both groups (HR 0.92; CI 0.70, 1.21 \( P=0.54 \)). Patient follow-up appointments did not differ significantly between groups (OR 1.26 95% CI 0.94, 1.70 \( P=0.29 \)).

**Conclusion:** This pragmatic trial tested the effectiveness of VisualDx on patient reported skin disease outcomes in a generalizable clinical setting. There was no difference in skin problem resolution or number of follow-up visits when PCPs used VisualDx.

**INTRODUCTION**

Physicians regularly refer to clinical evidence technologies (CETs) such as PubMed/MEDLINE, journal articles, electronic texts, topic summaries, and internet search engines to increase medical knowledge, improve diagnosis and treatment decisions [1-4]. Despite provider-reported benefits of CETs, and one observational study [5] that showed a reduction in length of stay in hospitals after subscribing to a CET, UpToDate, few studies have evaluated the impact of CETs on patient outcomes.

Medical Centers purchase or license CETs to support the education and patient care information needs of clinicians, and trainees. Unfortunately, CET licenses can be expensive.
Medical school libraries associated with teaching hospitals in the US or Canada spent an average of $US 2 million each in 2015 for medical research journals and clinical information resources [6]. Despite their cost, CETs have not received the rigorous evaluations that form the evidence base for other clinical technologies. A 2015 systematic review of interventions to increase health use of electronic health information including CETs by health care providers found no randomized trials with patient outcomes, such as relief from symptoms or utilization [7].

The broad nature and diverse goals of many CETs may discourage rigorous evaluation. However, skin conditions are a relatively circumscribed domain within the broad field of Primary Care. The clinical goal in most cases can be quantified as time to problem resolution. Likewise, the need for additional medical care after the index visit represents a suboptimal and expensive outcome that might be reduced by improved provider knowledge and decision support [8].

Skin problems account for 15% of primary care office visits in the U.S [9] and 8% of all outpatient visits for skin problems result in referrals to dermatologists or return visits to primary care [10]. Deficiencies in the ability of Primary Care Providers (PCPs) to diagnose skin rashes and lesions correctly have been noted in the literature [11] [12]. These studies indicated that additional dermatology knowledge and diagnostic support could improve patient outcomes. General Practitioners in the UK who used an online skin-cancer diagnosis information source increased their diagnostic accuracy and confidence, but did not reduce referrals [13].

VisualDx [15] is a CET that presents images and text on a broad range of skin conditions. Users may search by specific condition or they may enter patient characteristics and examination findings to generate a differential diagnosis list. It has been shown to improve the differential diagnosis of cellulitis by Emergency Room physicians, but that study did not assess patient
outcomes [14]. Individuals, practices, and institutions license VisualDx to support patient care [16].

We observed that VisualDx was not heavily used by clinicians in the study setting, allowing the possibility of finding adequate numbers of PCPs willing to submit to random assignment. Therefore, our objective was to evaluate the impact of VisualDx on patient outcomes (time to resolution) and utilization (return appointments) for skin problems, in a pragmatic randomized clinical trial in primary care. Recognizing that in typical clinical care, the correct diagnosis and therapy are often uncertain, that some problems resolve regardless of whether the management was technically correct, and that some resist even the most insightful management, we are concerned in this study with the net result of the episodes of care – the patient outcomes – rather than the intermediate steps of management.

METHODS

Model and Setting

The model underlying the design of the experiment asserts that the CET supports the PCP in management (diagnosis, treatment, and referral decisions). Presumably, a valuable CET leads to more correct diagnoses and wiser therapeutic or referral choices. These, in turn, lead to better patient outcomes (quicker resolution of the presenting problem and reduced need for additional care). To test this model, we performed a pragmatic randomized-cluster controlled trial of the impact of one CET, on the outcomes of skin problems presenting to Primary Care (Figure 1)
The study was conducted at clinics associated with an academic regional medical center in the Northeast. VisualDx and other CETs were available to medical center clinicians through the hospital Intranet, electronic health record (EHR), and mobile devices. The Institutional Review Board approved the protocol June 2015.

**Provider Subjects**

Attending physicians, residents, advanced practice nurses, and physician assistants in outpatient Family Medicine and General Internal Medicine were invited to participate by email or personal contact. Eligible providers 1) were currently seeing patients at a Primary Care site, 2) consented and agreed to comply with the protocol procedures assigned, and, 3) permitted patients to be informed of the study via a letter sent over their signature. Providers answered a survey concerning resident/attending status, year of clinical degree, sex, specialty, and typical
number of times per month they used CETs for patient care. (See Supplement 1: Provider Survey)

We randomly assigned PCPs to intervention or control groups using a sequential numbered envelope method stratified by resident status [17]. We randomized residents independently because of the possibility that they respond differently to the intervention than more experienced providers.

Providers were enrolled in the study when they provided consent, completed the tutorial and reaffirmed their agreement to follow the assigned protocol.

**Patient Subjects**

Adult patients seen for acute or chronic skin problems, excluding lacerations or burns, were eligible. Patients were excluded if non-English speaking or decisionally impaired. To identify patients, investigators reviewed the appointment records of participating providers for patients seen for a skin problem, based on reason for visit, provider notes, or ICD diagnosis codes. We sent each identified patient a letter signed by their PCP describing the study and informing them that the study team would call to invite their participation. The letter also stated how to opt out of any contact.

**Intervention**

The intervention was VisualDx as used by PCPs treating patients with skin problems. PCPs were randomly assigned to either the intervention group or the control group. Providers received email notification of their experimental group status with a link to a self-paced slide tutorial specific to their group. For the Active group, the 10-minute tutorial included the direction to use VisualDx when needed in treating a patient skin problem, and how to access and use it.
For Control providers, the tutorial included the direction not to use VisualDx, and a general orientation to information sources available through the Medical Library.

A study team member, not blinded to PCP assignment, contacted participating providers by email, phone, and letter at intervals during the study to remind them of their assigned protocol, and to re-confirm their participation.

**Measurements**

The primary predictor variable was the group status of the provider: Active (use of VisualDx) or Control (non-use). Patient subjects were assigned to the randomized group of the provider they saw. The primary outcome variables reported by the patients were: 1) time to resolution of the skin problem from presentation at the primary care office visit and 2) number of follow up visits (to any provider) for the same problem.

About 30 days after the index visit, an investigator phoned each eligible patient (except those who had opted out) and, following verbal consent, proceeded with the interview questions. If the patient reported their presenting skin problem resolved, their participation in the study was concluded. Patients whose presenting complaint had not resolved were re-interviewed at 60 days and, if still unresolved, again at 90 days. At the first interview, patients reported their age, sex, and whether the PCP seen was their usual provider. (See Supplement 2: Patient interview instruments.)

We ascertained the status of the skin problem as “All better”, “Improved,” Unchanged”, or “Worse”, each time we interviewed the patient. If “All better” at any interview, we asked them to state the number of days from the index visit date to when they realized the problem was resolved. This determined the “days to resolution” outcome data. If the problem was not resolved
by the first interview, we interviewed the patients at 60 days, and if still not resolved, at 90 days. The final problem status at the last completed interview was determined for analysis.

For the number of follow-up appointments, we asked how many appointments the patient had for the same problem since the index visit. If there was a second or third phone interview, we asked how many appointments they had since the last call. The total number of appointments reported comprised the variable.

**Data Collection**

Trained research assistants using standardized scripts conducted patient interviews by telephone. Study data were collected and managed using REDCap (Research Electronic Data Capture) secure tools hosted by the researchers’ institution [18].

**Blinding**

By necessity, providers knew their own intervention or control group status. Investigators were blind to providers’ and patients’ group while conducting patient interviews. Patients were blind to the group assignment of their provider.

**Analysis**

We used Cox proportional hazards models to assess time to resolution and Wilcoxon-rank sum tests and logistic regression to compare return appointments between groups. All logistic and proportional hazards models were adjusted for clustering. Data analyses were performed using Stata 14 statistical software [19]. We sought an adequate sample size to detect a moderate-to-large effect of the intervention, on the order of 0.4 standard deviations. Given the broad range of skin problems presenting in Primary Care, we expected significant variability in
the time to resolution. Therefore, we chose a target of 8 days in time to resolution with a standard
deviation of 20 days. The effect of clustering within PCP was not known, but we used estimates
from other primary care settings that suggested an intra-cluster correlation (ICC) of
approximately 0.025 \cite{20}. Assuming alpha = 0.05, beta = 0.80, 10 patients per provider, and a
two-sided t-test, we estimated the study needed 26 PCPs and 260 patients.

RESULTS
We enrolled 31 physicians and 1 nurse practitioner. We identified 989 eligible patients with a
skin problem visit to a participating PCP between November 2015 and August 2016. 433 patients
consented and provided data. (Figure 2)
Figure 2 Flow of participants through stages of the randomized-cluster controlled trial

The active and control groups were similar at baseline except for the median number of subjects per PCP (6 in the active group vs. 15 in the control group; $P=0.045$). (Table 1)
Table 1 Characteristics of Primary Care Providers and Patients

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Active</th>
<th>Control</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Care Providers, n</td>
<td>32</td>
<td>17</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Residents</td>
<td>13 (41%)</td>
<td>8 (47%)</td>
<td>5 (33%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>17 (53%)</td>
<td>10 (59%)</td>
<td>7 (47%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Family Medicine (vs. Internal Medicine)</td>
<td>14 (45%)</td>
<td>6 (35%)</td>
<td>8 (53%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Study patients per provider, median (range)</td>
<td>13.5 (1-34)</td>
<td>6 (1-32)</td>
<td>15 (1-34)</td>
<td>0.045</td>
</tr>
<tr>
<td>Used any CET≥10 times prior month</td>
<td>27 (84%)</td>
<td>13 (77%)</td>
<td>14 (93%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Used VisualDx prior month (yes)</td>
<td>7 (22%)</td>
<td>3 (18%)</td>
<td>4 (27%)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Patients, n

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Active</th>
<th>Control</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median (range), 431 obs.</td>
<td>58 (19-94)</td>
<td>58 (20-91)</td>
<td>58 (19-94)</td>
<td>0.73</td>
</tr>
<tr>
<td>Sex (male), 431 obs.</td>
<td>214 (49%)</td>
<td>77 (49%)</td>
<td>137 (50%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Completed all protocol interviews</td>
<td>360 (83%)</td>
<td>126 (80%)</td>
<td>234 (85%)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Unless noted, all cells contain n and (%). *P-value comparing Active and Control groups from X² tests for categorical variables (proportions) and Wilcoxon Rank-Sum tests for ordinal and continuous variables.

Problem Resolution

48% of all patients in the study considered their skin problem resolved (“All better”) by the final contact, including 46% in the active group and 49% in the control group (P=0.48). Active and control patients were similar in terms of whether they were “All better”, “Improved”, “Unchanged” or “Worse” at their final interview (P=0.88). (Table 2)
Table 2 Problem resolution and return visit outcomes

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Active</th>
<th>Control</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>433</td>
<td>158</td>
<td>275</td>
<td>0.88</td>
</tr>
<tr>
<td>Final skin status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolved</td>
<td>207 (48%)</td>
<td>72 (46%)</td>
<td>135 (49%)</td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>104 (24%)</td>
<td>41 (26%)</td>
<td>63 (23%)</td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td>108 (25%)</td>
<td>40 (25%)</td>
<td>68 (25%)</td>
<td></td>
</tr>
<tr>
<td>Worse</td>
<td>14 (3%)</td>
<td>5 (3%)</td>
<td>9 (3%)</td>
<td></td>
</tr>
<tr>
<td>Return visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Return visits per patient, mean (standard deviation)</td>
<td>0.59 (1.07)</td>
<td>0.65 (1.10)</td>
<td>0.55 (1.05)</td>
<td>0.19</td>
</tr>
<tr>
<td>Any return visits (vs. none)</td>
<td>148 (34%)</td>
<td>59 (37%)</td>
<td>89 (32%)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Unless noted, all cells contain n and (%). *P-value comparing Active and Control groups from $\chi^2$ tests for categorical variables (proportions) and Wilcoxon Rank-Sum test for number of visits.

Time to resolution was similar in the two groups throughout the observation period of up to 120 days ($P = 0.56$ by log-rank test). (Figure 3) In univariable Cox proportional hazards modelling, with standard errors adjusted for provider clusters, the days from index visit to resolution were similar in both groups (HR 0.92; 95% CI 0.70, 1.21; $P = 0.54$). Tests for potential confounding by patient age and sex, PCP status (as resident and as patient’s regular provider), PCP time since graduation, number of subjects per provider, and time of the year, indicated no potential confounding. Therefore, these variables were not included in the analysis.
Active group patients had a mean of 0.65 return appointments compared to 0.55 in the control group ($P=0.19$). Median was 0 return appointments in both groups (range 1-7). (Figure 3)
Thirty-seven percent of active patients had one or more follow-up appointments for the index problem vs. 32% of control, \( P=0.29 \). When analyzed as a binary variable (any follow-up visits vs. none) in cluster-adjusted logistic regression, the odds of a return visit in active group patients were higher than in the control group (OR 1.25; 95% CI 0.93, 1.67; \( P=0.15 \)) but were not statistically significant. Tests for potential confounding by patient characteristics (age and sex), PCP characteristics (as resident, as patient’s regular provider, and time since graduation) or time of the year indicated no confounding. Therefore, these variables were not included in the model. However, number of patients per provider was associated with both the use of any
follow-up visits ($P=0.066$) and group assignment ($P=0.065$) raising the possibility of confounding and was included in the final logistic regression model. The odds of any follow-up visits remained higher in the active group than the control group when adjusting for clustering and the number of subjects per provider (OR $= 1.14$, 95% CI $0.84, 1.56$; $P=0.39$), but was not statistically significant. The intra-cluster correlation coefficient (ICC) for both outcome measures was $<0.00001$ with an upper 95% confidence limit of 0.039.

**DISCUSSION**

Patients with skin problems whose PCPs used the CET VisualDx experienced similar rates of problem resolution and similar days to resolution as patients whose providers did not use it. There was no difference in the number of follow-up visits to any health-care provider for the index skin problem.

The goal of this study was to assess effectiveness of the CET as used in a generalizable clinical setting, rather than to determine its mechanism of action or efficacy under ideal conditions. Therefore, we designed a “pragmatic trial” in a clinical environment in which day-to-day factors were not highly controlled. Pragmatic trials seek to answer the question “Does this intervention work under usual conditions?”[21]. Intervention PCPs had flexibility in how they followed their assigned protocol to reference VisualDx when a patient care uncertainty arose. They could have searched within VisualDx by diagnosis terms, as opposed to using the differential diagnosis support tool. They could also decide that assistance was not needed with some patients and opt not to refer to the technology. They could seek advice from additional sources after consulting VisualDx. Nevertheless, we did encourage provider adherence to the
protocol. When contacted, all providers confirmed they were staying within their assigned protocol, to use VisualDx as a reference or not.

We obtained data for the primary outcomes from patient report because we sought to understand the outcome of care as the patient experienced it; we did not evaluate whether the diagnosis or treatment decided upon by the PCP was correct by some objective standard. Likewise, we did not distinguish appropriate follow-up appointments or referrals from unnecessary or avoidable ones, recording only that a follow-up occurred.

That providers seek information from clinical evidence sources to resolve uncertainties arising in patient care is well-documented. Ely, observed that providers sought information for 55% of their uncertainties [22]. Similarly, 84% of PCPs in the current study reported using CETs for patient care 10 or more times per month.

Physician-reported benefits of referring to CETs, such as correct diagnosis, treatment, and avoidance of adverse events have been noted previously [1-4, 14]. Marshall et al. in multi-institutional survey of physicians (n=4,906) and residents (1,290) in 118 hospitals, found that 36% of physicians and 42% of residents changed a diagnosis after referring to a clinical evidence source in a recent recalled incident [4]. Physicians (29%) and residents (32%) also reported avoidance of unnecessary procedures or tests because of the information they used in the incident.

Use of VisualDx may improve diagnostic skills. A team including the developer of VisualDx reported that among 28 cases initially misdiagnosed as cellulitis in the Emergency Room, VisualDx included the correct diagnosis in its differential diagnosis list more often than the admitting medical resident (64% vs. 14%; \(P=0.003\)) [14]. In a pilot study by Chou, clinical diagnoses of 13 patients were made by 13 dermatology residents and 51 medical students before
and after using VisualDx. Diagnostic accuracy increased from 63% to 81% (*P* <0.01) as judged by a consultant dermatologist [23]. Despite these positive intermediate effects, the published literature provides no evidence of better patient outcomes in the clinical setting, including the study reported here. Why did use of VisualDx, a technologically sophisticated, well-designed, state-of-the-art CET, fail to influence the tested outcomes for skin disease?

This study tested the effectiveness of VisualDx for the problem resolution and return visit outcomes, not for other outcomes such as improved diagnosis or satisfaction with care.

Some general reasons for failure were obviated by the design of the intervention. All active group PCPs were made aware of the resource, what it was meant to do, and how to access it. They received more training in its features than is usually available in clinical practice. Although the VisualDx interface appears intuitive and easy to use compared to other CETs (PubMed/MEDLINE for example), it is possible that PCPs found it difficult to find the information they needed. The specific content of VisualDx, written largely by specialists, could be inappropriate for the Primary Care setting. This may have contributed to busy clinicians bypassing VisualDx at times, resulting in suboptimal management. Even if the content is correct from a biomedical point-of-view, PCPs are not obligated to follow it. Indeed, local availability of certain procedures, prescriptions, and specialty referrals may make it reasonable to not follow the advice of the CET. Finally, it is possible that many skin problems presenting in Primary Care are inherently resistant to management no matter how well-informed. They will resolve (or not) at their own pace regardless of the diagnosis and therapy offered.

VisualDx is a costly CET, and this study may help health care organizations determine whether this resource is beneficial to clinical decision-making and patient outcomes where other
costly and equivalent evidence technologies are available, or, conversely, where there are few evidence resources.

**Strengths and Limitations**

The randomized cluster parallel design reduced the likelihood of bias due to differences in the provider and patient subjects. Secular events occurring outside the study, such as seasonal changes in skin-related appointments, affected providers and patients in the intervention and control groups equally because of the randomized, parallel design.

The study took place in one large academic medical center, possibly reducing generalizability to smaller hospital settings or to settings with a more diverse patient population. The characteristics of the patient population of the medical center and the rural Northeastern state where the research took place are similar to populations in rural regions of the United States in terms of age, race, poverty rates and other factors[24].

Although this is the largest randomized study of patient outcomes of use of a CET to date, the power to detect a potential effect was limited. Given the sample size of 433 patients, a control rate of resolution of 49% within 90 days, and assuming $\alpha=0.05$, the study had 80% power to detect a resolution rate of at least 63% in the active group using Chi-square analysis. The observed rate was 46% and therefore not significantly different from control. In the Cox model, the observed Hazard Ratio of 0.92 (favoring control) was well under the minimum detectable HR of 1.24. Likewise, the study had 80% power to detect a difference of 0.30 return visits per patient. The observed rate was 0.10 higher in the Active group. Given that all analyses showed a trend towards worse outcomes in the Active Group, it highly unlikely that a larger study would have demonstrated a statistically significant beneficial effect.
The study relied on provider adherence to the protocol based on their agreement to do so and their periodic confirmation. We did not have independent confirmation of their adherence. There may also have been contamination of knowledge of the intervention between provider subjects since there were active and control providers in some clinics. These issues are typical of pragmatic trials in which an effect in a real-world setting is tested.

The study relied upon the memory of patients for the reported outcome data. The first patient interviews followed the index office visit by approximately thirty days, a relatively short time span. Only one patient who consented could not remember the skin problem visit at all and was therefore ineligible for analysis. This study included patients with both acute and chronic conditions reflecting the usual variety of skin conditions seen in primary care. Patients may have reported well-managed chronic conditions as “improved” rather than as “all better”, thereby reducing the likelihood of a positive difference and possibly masking a positive result. However, when the final status “Improved” was combined with “All better” and analyzed, there was no difference between groups in the proportion of the outcome. Still, it is possible that a study of only acute or emergent skin conditions might have had a different outcome.

This was not a comprehensive multi-attribute assessment of the CET. Other attributes such as ease of use and usefulness were beyond the scope of this evaluation, but are being evaluated in further qualitative research.

**Implications**

Dermatology problems represent a large burden of disease in the U.S. population and this study elucidated the impact of one clinical evidence technology on relief of symptoms and return appointments. While this resource did not make a difference in these patient outcomes, it may have value for other goals such as medical knowledge, decision confirmation, and diagnostic
confidence. This pragmatic experimental methodology with patient-reported outcomes proved to be feasible and could be extended to evaluate other clinical evidence source technologies relevant to health care.

CONCLUSION

The study showed no difference in resolution of symptoms and return visits patients of doctors who referenced VisualDx. Although CETs may support other institutional missions, VisualDx does not appear to improve patient outcomes for skin problems managed in Primary Care.

REFERENCES


https://www.visualdx.com/visualdx/7/


19. StataCorp: Stata Statistical Software: Release 14 College Station, TX: StataCorp LP; 2015.


TRIAL REGISTRY: ClinicalTrials.gov: NCT02922738

AUTHOR CONTRIBUTIONS: MB and BL developed the study design and methods, MB conducted participant recruitment and data collection, MB and BL analyzed the data, interpreted it, and wrote and approved the final manuscript.

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