Diagnostic Delay in Breast Disease

A System Analysis of a Public Urban Hospital

Philip Wall, MD; Carol Moore; Mahmoud El-Tamer, MD; James J. Reilly, MD, MPM

Objective: To analyze the diagnostic process in 146 women referred to a breast clinic in an urban setting between January 1, 1994, and December 31, 1996.

Design: We devised the “diagnostic delay index (DDI),” defined as the time between the medical system’s awareness of a diagnostic need and the completion of the diagnostic process. The time awaiting breast clinic consultation and the diagnostic events experienced—including clinic visits, imaging studies, and biopsies—were recorded. We stratified patients in 2 pathways (palpable masses and mammogram-identified lesions) and by benign or malignant outcome.

Results: Patients in pathways 1 (n = 85) and 2 (n=61) had a mean (±SD) DDI of 68.4 (±46.9) days and 71.9 (±35.2) days, respectively. Patients in both pathways who had a malignant outcome had a significantly lower DDI than those who had a benign outcome (47.5±30.9 days vs 78.6±42.6) (P<.001); this advantage was most pronounced in patients with palpable lumps. The average patient waited more than 3 weeks for both an initial clinic consultation and operating room access. Quartile analysis of the DDI revealed statistically significant differences in clinic access time, number of visits, diagnostic events per visit, and operating room access time. Regression analysis demonstrates the relationship between DDI and measured process variables: DDI = -21.11 + 0.09 age + 1.86 pathway - 12.18 outcome + 1.08 clinic access + 11.91 visits + 0.94 operating room access (R²=61.5%).

Conclusions: In a public hospital, diagnostic delay is related to inadequate access to surgical consultation and a delay in operating room access. Regression analysis demonstrates the relationships between these components of system diagnostic delay and suggests strategies for reducing the DDI.

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The early diagnosis of disease is an established tenet of medicine in North America. Early diagnosis should enable early treatment, with the expectation of an improved outcome. The concept of early diagnosis is particularly pertinent for malignant disease. Efforts to speed the diagnosis of breast cancer have focused on regular mammographic screening and periodic breast self-examinations. Such techniques aim to detect tumors at an early stage, when treatment can be expected to lead to a better outcome.

A diagnostic delay may be due to a mix of patient and system factors. Many studies of patient factors have been conducted, but few have examined the process by which physicians diagnose breast disease and how physician and health system practices influence the speed with which a diagnosis is made.

In this retrospective study, we analyzed the experience of a large urban breast clinic at a public hospital in the early diagnosis of breast disease. The study focused on the diagnostic process and the resources used to make a diagnosis of benign or malignant breast disease.

The Breast Clinic of the Kings County Hospital Center, Brooklyn, NY, is a surgical specialty clinic that was established decades ago to provide outpatient care to patients with breast cancer. The clinic’s focus has shifted to include the diagnosis and treatment of benign breast disorders. The clinic’s appointment system keeps several appointment slots available for “high risk of malignancy” patients, who are given a “next available” appointment, usually within 1 week. The clinic’s patient population is derived through referrals from other clinics at the hospital, including an emergency department and urgent care center, and remote diagnostic and treatment centers. Patients are also self-referred.
PATIENTS AND METHODS

We examined retrospectively the medical records of 146 women visiting the breast clinic for the purpose of diagnosing breast disease in January 1, 1994, to December 31, 1996. All patients underwent at least 1 biopsy. Patients with breast abscesses or other inflammatory disorders and simple cysts were excluded. Patient information, including age and menopausal status, was recorded. Data were entered into a relational database program (Microsoft Access, version 2.0, Microsoft Corp, Redmond, Wash) and analyzed with commercially available statistical software (Mini-Tab 5.1.1, Mini-Tab, Inc, State College, Pa).

DIAGNOSTIC DELAY INDEX

For the purposes of this study, we defined the relevant time as the “diagnostic delay index (DDI).” This period began, by definition, on the date on which the medical care system at Kings County Hospital Center first became aware of a diagnostic need for each patient. For some patients, the DDI began on the date when an abnormal mammogram was obtained. For others, the DDI began when the patient sought care at a Kings County Hospital Center clinic with a symptom related to breast disease. The DDI terminated on the date on which the patient’s diagnosis was established and made known to the patient. This patient-centered time measurement reflects, we think, a relevant interval with regard to measuring the medical care system’s performance in establishing a clearly defined task, ie, making a diagnosis.

During the DDI, diagnostic events occurred while patients visited the hospital for consultations, imaging studies (mammography and ultrasonography), and biopsies. Events occurred during visits identified by a unique date. In some instances, several events occurred during a single visit (eg, a patient undergoes a mammogram, an ultrasonography, and a biopsy in the radiology department during a single visit). The ratio of events to visits is a measure of the efficiency of the diagnostic process. Patients had a waiting time for the initial breast clinic evaluation, which we designated the “clinic access” time. Those patients who underwent open biopsy in the operating room (OR) had a waiting time designated the “OR access” time.

Biopsies were performed in 3 venues: the radiology department under ultrasonographic guidance; the breast clinic, where palpable lesions were biopsied using a core needle or aspirated with a fine needle (or both); and the OR, where open excisional, incisional, and needle-localized biopsies were performed. All OR biopsies were performed on an ambulatory surgery basis. Scheduling a surgical procedure involves a complex process that includes anesthesia needs assessment; laboratory, radiological, and electrocardiographic testing; and the process of financial clearance. This last process assesses the insurance status of a patient before a biopsy is done. Approximately 50% of our patients were insured through public programs (Medicaid or Medicare), and for many of these patients, the Kings County Hospital Center applied for insurance during the diagnostic procedure. Of the 146 study patients, 71 (48.6%) were uninsured or “self-pay” patients.

PRESENTATION PATHWAYS

Patients presented to the health care system by 2 generally distinct pathways. Patients in pathway 1 reported a palpable breast mass. Patients in pathway 2 had an abnormal mammogram reading. In most of these patients, no palpable abnormality was observed, but in some, a mass lesion was identified. For all patients in pathway 2, the DDI began on the date on which the abnormal mammogram reading was obtained. Most patients in pathway 1 were either self-referred or referred from another Kings County Hospital Center clinic.

Patients were stratified by age into 3 categories: early reproductive (16-35 years), late reproductive (36-50 years), and menopause (>50 years). The outcome of the diagnostic process was classified as either benign or malignant, based on the histological assessment of the biopsy specimen.

RESULTS

PATIENT CHARACTERISTICS

We identified 146 patient records to analyze for this study. Ages ranged from 16 to 78 years, with a mean (±SD) of 45.2 (±16.6) years. The age distribution and malignant outcome by reproductive category are presented in Table 1. The mean (±SD) DDI for all patients was 69.8 (±42.2) days (Table 2). Patients with malignant outcomes had a shorter DDI than patients with a benign outcome (45.7±30.9 vs 78.6±42.6) (P<.001).

Patients experienced numerous events during the DDI (Table 3). These events, which included clinic visits, biopsies, and imaging studies, differed by the presentation pathway. Patients in pathway 1 made more clinic visits (2.9±1.2 vs 2.3±0.9 [mean ± SD]) (P<.01) and had more biopsies (1.9±0.8 vs 1.2±0.5) (P<.001). Patients in pathway 2 had more diagnostic imaging studies (1.2±0.6 vs 0.9±0.8) (P<.01).

The mean (±SD) clinic access wait for all patients was 24.4 (±22.3) days. We observed no difference between patients in pathways 1 and 2 (23.7±23.3 days vs 25.2±21.4 days) (P=.48). For all patients, the mean (±SD) OR access time was 26.6 (±18.2) days. For patients in pathway 2, the scheduling process is complicated by the need to coordinate the OR schedule of the mammography facility for needle localization biopsies. Nonetheless, the OR access time for patients in pathway 1 with a palpable lesion (25.2±18.9 days) did not differ from that of the patients in pathway 2 (26.1±15.0 days) (P=.84).

The large DDI SDs reflect substantial variation within our stratified groups (Figure). To understand this variance, we stratified patients by DDI quartiles and compared presentation pathways with regard to diagnostic events, visits, and access times (Table 4). Patients with palpable disease were relatively overrepresented in the lowest DDI quartile compared with those with abnormal mammograms. A similar overrepresentation of patients with a malignant outcome was noted here as well.
Hospital in New York City. The DDI is a clinically rel-
diagnosing breast disease, is performed at a large public
This study analyzes the processes by which a specific task,
multivariate regression analysis using pathway, out-
tient-related variable coefficients were statistically insig-
patients in the longest DDI quartile proved to have
From the first to the fourth quartile, patients had pro-
tients underwent more diagnostic events and made more
Efficiency declined across quartiles, reflected by the events-
Finally, across quartiles, patients had progressively longer waiting times for OR open biopsies.

REGRESSION ANALYSIS
To explore the predictive relationship between several
we performed multivariate regression analysis using pathway, outcome, clinic access, visits, and OR access as the predic-
Both pathway and outcome were
Although a malignant neoplasm was diagnosed most fre-
Frequency in patients in the first 2 DDI quartiles, 11% of
Patients were system variables.

Table 1. Diagnostic Outcomes of Patients Attending
a Breast Clinic, by Pathway and Age Group

<table>
<thead>
<tr>
<th>Patient Classification*</th>
<th>Benign</th>
<th>Malignant</th>
<th>All, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathway 1</td>
<td>65</td>
<td>20</td>
<td>85 (58.2)</td>
</tr>
<tr>
<td>Pathway 2</td>
<td>42</td>
<td>19</td>
<td>61 (41.8)</td>
</tr>
<tr>
<td>All</td>
<td>107</td>
<td>39</td>
<td>146 (100.0)</td>
</tr>
<tr>
<td>Childbearing</td>
<td>36</td>
<td>3</td>
<td>39 (26.7)</td>
</tr>
<tr>
<td>Perimenopause</td>
<td>41</td>
<td>6</td>
<td>47 (32.2)</td>
</tr>
<tr>
<td>Menopause</td>
<td>30</td>
<td>30</td>
<td>60 (40.1)</td>
</tr>
<tr>
<td>All</td>
<td>107</td>
<td>39</td>
<td>146 (99.0)</td>
</tr>
</tbody>
</table>

*See “Presentation Pathways” subsection of the “Patients and Methods” section for a description of the pathways and definitions of age groups.

Table 2. Diagnostic Delay Index (DDI), by Outcome and Pathway

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Benign†</th>
<th>Malignant‡</th>
<th>All§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>79.7 ± 46.3</td>
<td>32.8 ± 27.8</td>
<td>68.4 ± 46.9</td>
</tr>
<tr>
<td>2</td>
<td>77.6 ± 36.6</td>
<td>59.3 ± 28.8</td>
<td>71.9 ± 35.2</td>
</tr>
<tr>
<td>All</td>
<td>78.6 ± 42.6</td>
<td>45.7 ± 30.9</td>
<td>69.8 ± 42.2</td>
</tr>
</tbody>
</table>

†OR indicates operating room.
‡The DDI by pathway and malignant vs benign outcomes both differ at P.<.001.

Table 3. Diagnostic Events and Access Times by Pathway

<table>
<thead>
<tr>
<th>Diagnostic Event†</th>
<th>Pathway</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic visits</td>
<td>1</td>
<td>2.9 ± 1.2</td>
</tr>
<tr>
<td>Biopsies</td>
<td>1.9 ± 0.8</td>
<td>1.2 ± 0.5</td>
</tr>
<tr>
<td>Imaging studies</td>
<td>0.9 ± 0.8</td>
<td>1.2 ± 0.6</td>
</tr>
<tr>
<td>Clinic access time</td>
<td>23.7 ± 23.3</td>
<td>25.2 ± 21.4</td>
</tr>
<tr>
<td>OR access time</td>
<td>25.2 ± 18.9</td>
<td>26.1 ± 15.0</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD.
†Data are given as mean ± SD.

COMMENT
This study analyzes the processes by which a specific task, diagnosing breast disease, is performed at a large public hospital in New York City. The DDI is a clinically relevant, patient-centered measure of this process. Al-
though our health care system successfully identified most patients with a malignant disease in relatively shorter DDIs, this advantage was most notable in those with palpable disease. The diagnostic task was more direct and thus consumed fewer days. We noticed 3 trends in the diagnosis of breast diseases: palpable malignant lumps, mammographic abnormalities that required a needle localization biopsy, and palpable benign lesions. The first group of patients had the shortest mean DDI (32.8 days). The clinic workup time of these patients can be calculated by subtracting the mean clinic access time from the mean DDI (32.8 – 23.7 = 9.1 days). The short clinic workup time is related to the fact that the diagnosis of a palpable lump was achieved by a core needle biopsy done initially at the first clinic presentation. The patients were generally informed of the diagnosis 1 week later at the next surgical clinic visit. Some patients had false-negative findings on the core needle biopsy and needed an open biopsy or a core needle biopsy under ultrasonographic guidance. Clearly, the addition of another diagnostic procedure as an operative biopsy or a biopsy under sonographic guidance will add at least 4 to 5 weeks for the completion of the diagnostic process. From this group analysis, it is obvious that to shorten the DDI of patients with palpable malignant lumps, we must shorten the clinic access time.

For the group with mammographic abnormalities, the mean DDI was significantly shorter for patients with a malignant outcome than for those with a benign outcome (39.3 vs 77.6 days). The mean clinic and OR access time for that group is 25.2 + 26.1 = 51.3 days, which accounts for 86.5% and 66.0% of the DDI for patients with a malignant outcome and those with a benign outcome, respectively. In the quartile subset analysis, we ob-
served that many patients with prolonged DDIs had a patient-related delay. Public hospitals deal with diverse patients with often dramatic psychological, social, and economic needs that markedly affect their health care. Diverse patient factors certainly were present in our study, and, doubtless, such patient-related factors lengthened many patients’ DDIs. When patients fail to schedule ordered tests, miss clinic appointments, or are unable to produce necessary residency or employment documents, the DDI increases. These patient-related factors resulted in frequent OR cancellations, prolonging further the OR access time. Identifying and quantifying these important factors in our retrospective study proved impossible. These unmeasured factors are doubtless embedded in our data and contribute to the unexplained error of our predictive DDI regression equation. Other factors that contributed to the delay were the frequent recalling of patients for more mammographic views to further evaluate lesions detected on screening mammograms.

The third group, those with benign palpable lesions, had the longest DDI. A subset analysis of these patients shows that most patients in the third or fourth DDI quartile were young women with clinical, sonographic, and frequently a core needle biopsy diagnosis of fibroadenoma. These patients are scheduled for excisional biopsy at a more leisurely pace that is convenient to the patient, her family, or both. The DDI terminated in these patients following the diagnosis by excisional biopsy; this may have prolonged their DDI. Some of these patients wanted a conservative watchful approach to their lesion but returned a few months later and consented to excision.

Modern health care quality concepts stress the importance of reducing variation in medical practice. We noted a striking variation in the DDI, reflected by the large DDI SDs of all patient groups. Quartile analysis identifies factors contributing to this variation. Patients in the lowest DDI quartile had shorter clinic access and OR access times, fewer diagnostic events and hospital visits, and a higher event-visit ratio than those in progressively higher DDI quartiles. Breast diagnostic centers concentrate the efforts of surgeons and radiologists by performing necessary diagnostic events in as few visits as possible, often during a single visit. Referral and treatment algorithms must be multidisciplinary and collaborative and involve primary care referring physicians, radiologists, and surgeons. Educating primary care physicians to deal with simple breast

### Table 4. Presentation and Diagnostic Variables by Diagnostic Delay Index (DDI) Quartile*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quartile 1 (0-42 d)</th>
<th>Quartile 2 (43-57 d)</th>
<th>Quartile 3 (58-96 d)</th>
<th>Quartile 4 (97-226 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50.1</td>
<td>49.2</td>
<td>45.1</td>
<td>39.3†</td>
</tr>
<tr>
<td>Pathway, % mammoogram</td>
<td>22</td>
<td>65‡</td>
<td>39</td>
<td>42</td>
</tr>
<tr>
<td>Clinic access, d</td>
<td>8.72</td>
<td>15.21†</td>
<td>26.3‡</td>
<td>44.6‡</td>
</tr>
<tr>
<td>Events, count</td>
<td>5.03</td>
<td>6.08</td>
<td>6.42‡</td>
<td>6.17†</td>
</tr>
<tr>
<td>Visits, count</td>
<td>3.47</td>
<td>5.05‡</td>
<td>5.28‡</td>
<td>5.26‡</td>
</tr>
<tr>
<td>Events/visit ratio</td>
<td>1.53</td>
<td>1.19‡</td>
<td>1.20‡</td>
<td>1.19‡</td>
</tr>
<tr>
<td>OR access, d</td>
<td>15.2</td>
<td>19.43</td>
<td>26.20‡</td>
<td>37.50‡</td>
</tr>
<tr>
<td>Outcome, % malignant</td>
<td>50</td>
<td>27</td>
<td>19†</td>
<td>11‡</td>
</tr>
</tbody>
</table>

*Data are given as mean unless otherwise indicated. OR indicates operating room.
†P < 0.01 compared with quartile 1 value.
‡P < 0.001 compared with quartile 1 value.

### Table 5. Regression Analysis*

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Coefficient</th>
<th>SD</th>
<th>T Ratio†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>−21.11</td>
<td>16.04</td>
<td>−1.32</td>
<td>.41</td>
</tr>
<tr>
<td>Age</td>
<td>−0.09</td>
<td>0.23</td>
<td>−0.43</td>
<td>.17</td>
</tr>
<tr>
<td>Pathway</td>
<td>1.86</td>
<td>7.47</td>
<td>0.25</td>
<td>.099</td>
</tr>
<tr>
<td>Outcome</td>
<td>−12.18</td>
<td>7.75</td>
<td>−1.57</td>
<td>.44</td>
</tr>
<tr>
<td>Clinic access</td>
<td>1.08</td>
<td>0.13</td>
<td>8.13</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Visits</td>
<td>11.91</td>
<td>3.75</td>
<td>3.18</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>OR access</td>
<td>0.94</td>
<td>15</td>
<td>6.43</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Diagnostic delay index (DDI) = −21.11 + 0.09 age + 1.86 pathway − 12.18 outcome + 1.08 clinic access + 11.91 visits + 0.94 operating room (OR) access; R² = 0.615.
†Test statistic for each variable.
problems allows breast clinics to concentrate on patients with more serious breast problems, hence, shortening the clinic access time. The dilemma of organizing such activities of a large urban teaching hospital is substantial but not insurmountable.

Because diagnostic events often occur “one at a time,” patients must make numerous hospital visits. Patients in the midst of a multivisit diagnostic process occupy available clinic appointments, constraining clinic access for new patients. The regression analysis predicts that reducing the number of visits dramatically lowers the DDI. A 1-stop breast center may concentrate the diagnostic procedures in 1 visit and dramatically decrease the DDI. Furthermore, if such a breast center has the capability of outpatient biopsies, the OR access time will also be reduced.

A clinic that meets only on a midweek afternoon poses considerable problems for many working women and mothers to attend. Designing a clinic system in which the working poor, mothers with young children, and those without private transportation can receive effective health care is a major challenge. Achieving diagnostic and therapeutic goals in a cost-effective manner is a high priority for all health care providers, but may be nowhere more difficult to achieve than those at a public hospital clinic.

Reprints: James J. Reilly, MD, MPM, Department of Surgery, Kings County Hospital Center, 451 Clarkson Ave, Brooklyn, NY 11203.

REFERENCES


JAMA

Bioequivalence of Generic and Brand-name Levothyroxine Products in the Treatment of Hypothyroidism

Betty J. Dong, PharmD; Walter W. Hauck, PhD; John G. Gambertoglio, PharmD; Lauren Gec, MPH; John R. White, PharmD; Jeff L. Bubp, PharmD; Francis S. Greenspan, MD

Objective.—To compare relative bioavailability of Synthroid, Levoxine (Levoxine has been renamed Levoxy), and 2 generic levothyroxine sodium preparations.

Design.—Single-blind (primary investigators blinded), randomized, 4-way crossover trial.

Setting.—Ambulatory care.

Patients.—Twenty-two women with hypothyroidism who were clinically and chemically euthyroid and were receiving levothyroxine sodium, 0.1 or 0.15 mg.

Interventions.—All patients received each of the 4 levothyroxine products for 6-week periods in the same dosage as their prestudy regimen with no washout period. The order of the drug sequences was randomly determined before study initiation.

Main Outcome Measures.—Area under the curve, time to peak serum concentrations, and peak serum concentrations of thyroxine, triiodothyronine, and free thyroxine index for all 4 products.

Results.—All data analyses were completed prior to unblinding of the product codes. No significant differences between the 4 products were found in area under the curve or peak serum concentrations of total thyroxine, total triiodothyronine, or free thyroxine index. Although Synthroid produced a more rapid rise in total serum triiodothyronine concentration and a higher total peak serum triiodothyronine concentration than the other products, these differences were not statistically significant (P=.08). The Food and Drug Administration criterion for relative bioequivalence within 90% confidence intervals (0.8-1.25) was demonstrated (P<.05) for all pairs of products. Relative bioequivalence of 0.95 to 1.07 was demonstrated, tighter than the current bioequivalence criterion for oral formulations.

Conclusions.—The 4 generic and brand-name levothyroxine preparations studied are different but are bioequivalent by current Food and Drug Administration criteria and are interchangeable in the majority of patients receiving thyroxine replacement therapy. Further investigation is required to determine whether our results are equally applicable to all existing levothyroxine preparations. JAMA. 1997;277:1205-1213

Reprints: Betty J. Dong, PharmD, Department of Clinical Pharmacy, University of California School of Pharmacy, C-152, 521 Parnassus Ave, San Francisco, CA 94143-0622.