



Special Section on Telepathology

Virtual slide telepathology enables an innovative telehealth rapid breast care clinic[☆]

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Summary An innovative telemedicine-enabled rapid breast care service is described that bundles telemammography, telepathology, and teleoncology services into a single day process. The service is called the *UltraClinics[®] Process*. Because the core services are at 4 different physical locations, a challenge has been to obtain stat second opinion readouts on newly diagnosed breast cancer cases. To provide same day quality assurance rereview of breast surgical pathology cases, a DMetrix DX-40 ultrarapid virtual slide scanner (DMetrix Inc, Tucson, AZ) was installed at the participating laboratory. Glass slides of breast cancer and breast hyperplasia cases were scanned the same day the slides were produced by the University Physicians Healthcare Hospital histology laboratory. Virtual slide telepathology was used for stat quality assurance readouts at University Medical Center, 6 miles away. There was complete concurrence with the primary diagnosis in 139 (90.3%) of cases. There were 4 (2.3%) major discrepancies, which would have resulted in a different therapy and 3 (1.9%) minor discrepancies. Three cases (1.9%) were deferred for immunohistochemistry. In 2 cases (1.3%), the case was deferred for examination of the glass slides by the reviewing pathologists at University Medical Center. We conclude that the virtual slide telepathology quality assurance program found a small number of significant diagnostic discrepancies. The virtual slide telepathology program service increased the job satisfaction of subspecialty pathologists without special training in breast pathology, assigned to cover the general surgical pathology service at a small satellite university hospital.

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[☆] Ronald S. Weinstein, MD, is a cofounder of DMetrix Inc and has equity in the company. Lynne C. Richter, MT (ASCP), has been a consultant to DMetrix and has equity. Dr Weinstein was scientific director of Apollo Inc from 2001 to 2005. He also founded UltraClinics Inc and has equity in the company.

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1. Introduction

Breast cancer is the second leading cause of cancer death for women in the United States. There is evidence that prompt entry into breast care can prolong breast cancer patient survival [1]. It is generally accepted that breast cancer screening with periodic clinical breast examinations, mammography, and breast biopsies are important components of the breast cancer detection process. It is estimated that 50 million mammograms are performed in the United States annually. Approximately 2% of women with mammograms will require a subsequent biopsy, most of which will be benign. Frank malignancy will be found in about 10% of the women who have undergone breast biopsies [2,3].

In the United States, breast care is typically quite fragmented. Patients may need to go to a number of different locations for physical examinations, breast imaging studies, biopsies, and appointments with breast care specialists. The Arizona Telemedicine Program, which was administratively housed in the Department of Pathology at the University of Arizona College of Medicine (Tucson, AZ) for many years, has experience in developing innovative health care delivery services leveraging telemedicine technologies [4-12]. As reported in this article, the faculty and staff of: the Arizona Telemedicine Program; The Arizona Cancer Center; and the Departments of Pathology, Radiology, and Medicine, of the University of Arizona College of Medicine, collaborated in developing an innovative rapid breast care process, the so-called Telehealth Rapid Breast Care Process or UltraClinics® Process. Fig. 1 represents the workflow for this process.

This process reduces fragmentation of breast care services by the following: (1) administratively linking previously semiautonomous diagnostic and clinical activities in the pretherapeutic phases of breast care; (2) using several telemedicine services (ie, telemammography, telepathology, and teleoncology) to eliminate the need for patients to travel to multiple locations for radiologic, laboratory, and oncological interventions, thus, creating a “virtual” point-of-care environment from the perspective of the patient because the

patient remains at a single location throughout the process; (3) implementing rapid breast core biopsy tissue processing and virtual slide telepathology case readouts, for immediate second opinions of breast core biopsies positive for cancer; (4) instituting same day reporting of imaging and laboratory testing to breast care specialists; and (5) electronically linking patients to breast care specialists, for purposes of informing patients of their diagnosis and initiating the development of a treatment plan. Telemedicine and telepathology may provide some solutions to this challenging breast care fragmentation problem [13-15].

Telemedicine and telehealth have the technologies to provide some solutions to the breast care fragmentation problems [9-14,16,17]. This article describes the laboratory components of the Telehealth Rapid Breast Care Process in detail, including validation studies for its laboratory procedures. Patient and provider satisfaction with the process has been high, as will be described in detail in a separate article (Lopez et al, in preparation). To date, more than 300 patients have participated in the rapid breast care program. This article focuses on an analysis of the laboratory component of the process for the first 154 patients [8,18].

2. Materials and methods

2.1. Preimplementation laboratory procedure validation

Development and validation of the laboratory components of the Telehealth Rapid Breast Care Process took place in phases as follows: a preclinical service implementation phase and a clinical service phase. We performed a preimplementation laboratory procedure validation study, before patients were enrolled in the program, and a second laboratory “validation” study, as part of the quality assurance program for the expedited breast care process clinical service. Both studies, reported in this article, were carried out before the American Society of Clinical Oncology/College of American Pathologists (CAP) guidelines recommendations for human epidermal growth factor receptor-2 (HER-2/neu) testing in breast cancer were published [19].

A preimplementation institutional regulatory board-approved laboratory validation study was carried out to examine the feasibility of performing breast marker studies (ie, ER (estrogen receptor), PR (progesterone receptor), HER-2) on 30-minute 10% neutral buffered formalin-fixed, rapidly processed breast tissue specimens. This was performed in the years 2004 to 2005 [19]. The validation methodology was in keeping with the CAP’s guidelines for laboratory test validation before initiating an alternative testing method in a laboratory.

Although breast marker studies are not offered as part of the Telehealth Rapid Breast Care Process as currently defined, this validation study on breast markers was

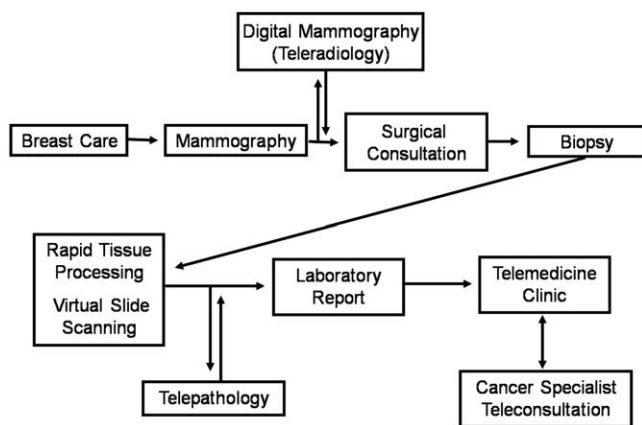


Fig. 1 Schematic of telehealth-enabled patient care services for the Telehealth Rapid Breast Care Clinic (UltraClinics Process).

performed to ensure that ER, PR, and HER-2/neu testing could be performed on breast tissue samples fixed for 30 minutes and rapidly processed into paraffin blocks.

Samples from 25 breast cancer surgical pathology specimens were used. From each specimen, a carefully dissected, approximately 1-mm thick slice of breast cancer tissue from a lumpectomy or mastectomy was fixed in 10% neutral buffered formalin for 30 minutes and then processed in a Milestone Medical Microwave Lab station (Model RHS-1, Milestone Medical Technologies Inc, Shelton, CT) [20-22]. A paired thicker (3-5 mm) slice of the breast surgical pathologic specimen was fixed in 10% neutral buffered formalin for 8 hours and processed overnight (Sakura Tissue Tek VIP, Sakura, Torrance, CA).

Paraffin-embedded tissue, either rapidly processed or routinely processed, was sectioned at 6- μ m thickness and stained with hematoxylin and eosin. All immunohistochemistry (IHC) for the breast markers ER, PR, Ki-67 and HER-2/neu was performed in a single laboratory, the University Medical Center laboratory, using the manufacturer-recommended protocol for breast marker immunostaining on a Benchmark XT Immunostainer (Ventana Medical Systems Inc, Oro Valley, AZ).

The breast marker slides were read by one observer (KMS), blinded as to the slide pairing. The scoring was based on staining intensity for each marker. A second, independent observer (ARG), blinded as to the first observer's scoring of the immunohistochemistry results, reread the slides 6 months or longer after the original readouts by the pathologist. Although there were minor differences in interpretations, interobserver variability in scoring of immunohistochemistry staining and in situ hybridization study results for the 25 cases were not significant in impact on clinical decisions for treatments.

After successful completion of this preimplementation validation study, patients were offered the same day telehealth rapid breast clinic services.

2.2. Accrual of telehealth rapid breast care patients

After the completion of preimplementation laboratory procedure validation, the telehealth rapid breast care service was then offered to patients at the University Physicians Healthcare's Tucson Breast Center (AZ) by the radiologist doing the mammography study. With this institutional regulatory board-approved service, core breast biopsy specimens were taken by courier from the Tucson Breast Center to 1 of 2 shared facilities for processing, the histology laboratory of the clinical laboratory at University Physicians Healthcare Hospital (10 miles away from the Tucson Breast Center) or University Medical Center (4 miles away from the Tucson Breast Center). Both university-affiliated hospital facilities have Milestone Microwave units and extensive experience handling rapidly processed biopsy specimens. To date, hundreds of surgical pathologic specimens have been

rapidly processed at each laboratory with Milestone Microwave units, including many breast biopsy specimens, renal biopsy specimens, and heart biopsy specimens.

2.3. Second Arizona rapid breast care laboratory validation study

Most Telehealth Rapid Breast Care Process patients had benign breast core biopsies, as would be expected for patients who underwent biopsy at a breast imaging center. Patients eligible for entry into the second rapid laboratory process "validation" study were the 32, of the initial 154 Telehealth Rapid Breast Care Process patients, who had a breast cancer diagnosis. All cancer diagnoses were verified by second opinions rendered by virtual slide telepathology. Of these 32 patients with biopsy-proven cancer, 30 patients met the laboratory validation study requirements of the following: (1) having both their breast core biopsies and their definitive lumpectomy or mammography surgery at University of Arizona-affiliated clinical facilities (ie, University Medical Center, University Physicians Healthcare Hospital, or the Tucson Breast Center) and (2) having the breast marker studies ER, PR, and HER-2/neu carried out on both their breast core biopsy specimens and the definitive surgical specimens. This enabled the direct comparison of breast core biopsy and surgical specimen breast marker test results. All of the immunohistochemistry studies were performed at a single immunohistochemistry laboratory, at University Medical Center in Tucson, AZ.

The core needle biopsy specimens from the telehealth rapid breast care patients were fixed in 10% neutral buffered formalin for approximately 30 minutes before rapid processing. These patients' subsequent lumpectomy or mastectomy specimens were received in the surgical pathology laboratory weeks later. The lumpectomy and mastectomy surgical pathologic specimens were fixed for 8 hours in 10% neutral buffered formalin before routine overnight processing.

For this diagnostic accuracy (validation) study, the same protocol as was used in the first validation was used for slide readouts, with 2 independent observers reading out the marker studies. This validation study differed from the first validation study in that the second observer's readouts were 2 to 4 weeks after the first observer's readouts. Again, the second case slide reviews for breast marker studies by a second pathologist yielded no clinically significant interobserver discrepancies in laboratory report results for the breast markers. Thus, marker study results for breast specimens fixed with 10% formalin for either 30 minutes or 8 hours were essentially interchangeable.

2.4. Virtual slide telepathology implementation for the telehealth rapid breast care service

As part of the Telehealth Rapid Breast Care Process, virtual slide telepathology is used for second opinions on

newly diagnosed breast cancer cases [8]. This quality assurance program is described in greater detail in a companion article in this mini-symposium, by Graham et al [23]. With regard to our implementation of the Telehealth Rapid Breast Care Process laboratory service, virtual slide telepathology has been used to address a specific pathology staffing problem. Although both of our University of Arizona-affiliated hospitals, which are staffed by the same faculty group practice, have Milestone rapid tissue processors, most of the breast core biopsies from the Tucson Breast Center were transported to the University Physicians Healthcare Hospital facility, 10 miles away from the Tucson Breast Center. The University Physicians Healthcare Hospital laboratory is staffed by a single part-time pathologist on-site [8]. Because our pathology practice requires second opinions on all new cancer cases, as the standard of care, obtaining immediate second opinions on breast cancer cases can be problematic. This was successfully addressed through the introduction of virtual slide telepathology and the capability to insert virtual slide telepathology cases into the ordinary workflow of the University Medical Center regularly scheduled 2:00 PM Quality Assurance Program, 6 miles away [8,23-29]. Virtual slides were produced with the DMetrix DX-40 scanner (DMetrix Inc, Tucson, AZ) that has also been described elsewhere [30,31]. The Quality Assurance program was implemented in 2006 and is described in a companion article [23].

2.5. Virtual slide telepathology-enabled quality assurance program

According to the Telehealth Rapid Breast Care Process laboratory protocol, the primary pathologist at University Physicians Healthcare Hospital generates a provisional written report based on light microscopy examination of the slides at the University Physicians Healthcare Hospital Laboratory. These are breast core biopsy specimens procured in the morning at the Tucson Breast Center, were immediately transported to the University Physicians Healthcare Hospital laboratory 10 miles away, stat processed into glass histopathologic slides, and read out by the single University Physicians Healthcare Hospital pathologist, typically by 1:30 PM the same day as the breast core biopsy taken at the off-campus imaging center. Then, at 2:00 PM each day, breast core biopsy cases, originating from University Physicians Healthcare Hospital and processed for virtual slide telepathology, were rereviewed at University Medical Center by a group of staff pathologists, pathology residents, and medical students, on a 50" plasma screen monitor using the DMetrix virtual slide viewer (Fig. 2). Second opinion reports were immediately sent by fax back to University Physicians Healthcare Hospital laboratory. From there, they are transmitted immediately to the oncologist on call for the Telehealth Rapid Breast Care Process service.

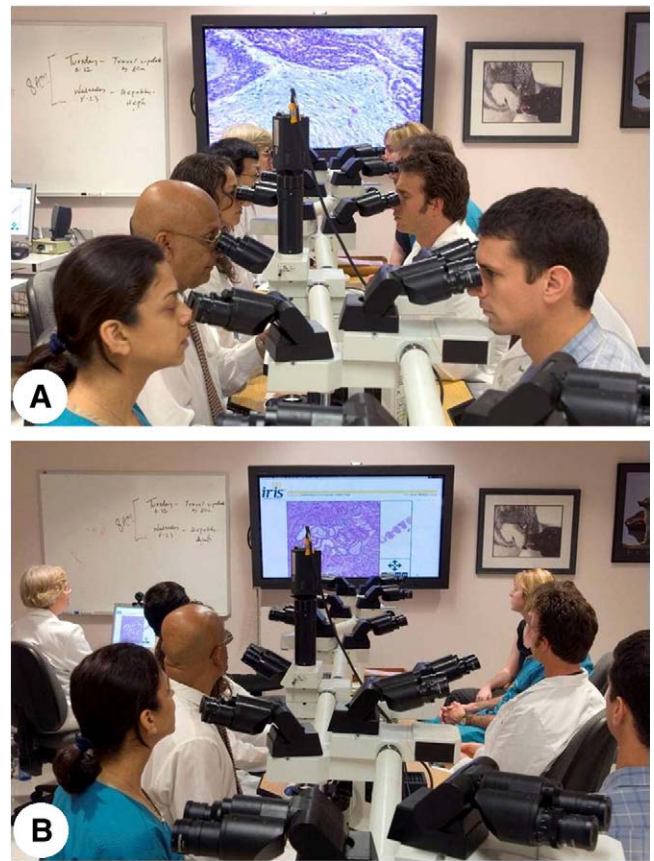


Fig. 2 (A) Pathology faculty and residents reviewing the current day's University Medicine Center surgical pathology cases for quality assurance around a 14-head light microscope. The image on the screen in the background displays the same microscopic image being viewed by the participants through the microscope. (B) Pathology faculty and residents stopping during the same daily University Medical Center surgical pathology quality assurance conference viewing a case being transmitted via virtual slide telepathology from the University Physicians Healthcare Hospital, 6 miles away. The image on the screen, in B, is the enlarged DMetrix Iris image capture partially seen on the small monitor to the (lower) left of the photograph. The virtual slide telepathology image on the large screen is being managed by the medical technologist (lower left).

2.6. Laboratory service timing study

Steps in the laboratory component of the Telehealth Rapid Breast Care Process, including second opinions by virtual slide telepathology, were carefully timed with a stopwatch for 10 consecutive cases, to establish a benchmark for the Telehealth Rapid Breast Care Process. Measurement of the total elapsed time for this laboratory component began when the surgeon or radiologist placed the breast core biopsy in formalin fixative. The time of the end point for the laboratory component was recorded when the written laboratory report, including a telepathology virtual slide-based second opinion for cancer cases, was available to the oncologist or surgeon for immediate discussion of the case with the patient by video conferencing or cell phone.

3. Results

3.1. Laboratory testing throughput efficiency

The average elapsed time for what is defined as the laboratory component of the Telehealth Rapid Breast Care Process (UltraClinics Process) was 3 hours and 22 minutes (ie, 202 minutes). Formalin fixation of the breast core biopsy specimens for 7 of 10 cases was between 32 and 38 minutes. Some of the outliers were attributed to start-up courier issues that have since been largely resolved.

Virtual slide manufacturing times included the time to carry the glass slides to the virtual slide scanning facility, to log the case in, and for the histotechnologist to examine the virtual slides on a local video monitor to insure they were representative of the glass slides and of good quality (ie, uniformity in focus, brightness, and others). Virtual slide production times, including the clerical and transport activities, ranged from 4 to 27 minutes. The receiving of telepathology second opinions took 1 to 70 minutes, from the time the virtual slides were stored on the DMetrix server until faxed written reports from University Medical Center were received at the primary laboratory at University Physicians Healthcare Hospital. On follow-up, this variability in quality assurance case turnaround times was largely attributed to virtual slide telepathology cases being inserted into the routine workflow of the daily Quality Assurance Conference of the busy surgical pathology service at University Medical Center laboratories, miles away in another part of Tucson. Virtual slide telepathology quality assurance second opinion turnaround times could be expedited by making these telepathology readouts an even higher priority. If these Telehealth Rapid Breast Care Process services were implemented by other organizations, the virtual slide telepathology second opinion readouts could be managed by a dedicated call center rather than inserting the cases into the workflow of a general pathology service. The actual viewing times for the telepathology virtual slides for a case and generation of a report, typically took less than 5 minutes. Insertion into the University Medical Center surgical pathology workflow was not regarded as being disruptive (Fig. 2). Faculty, residents, and students valued being part of this state-of-the-art virtual slide telepathology service and often shared their experiences with telepathology with candidates for University Medical Center's pathology residency program. The monitor image quality was deemed to be high, satisfactory for diagnostic interpretations and teaching (Fig. 3).

3.2. Laboratory procedure validation studies

In both validation studies, morphologic detail for hematoxylin and eosin-stained slides and immunohistochemistry slides were rated as good, or slightly better, in the rapidly fixed, rapidly processed tissue as compared with the

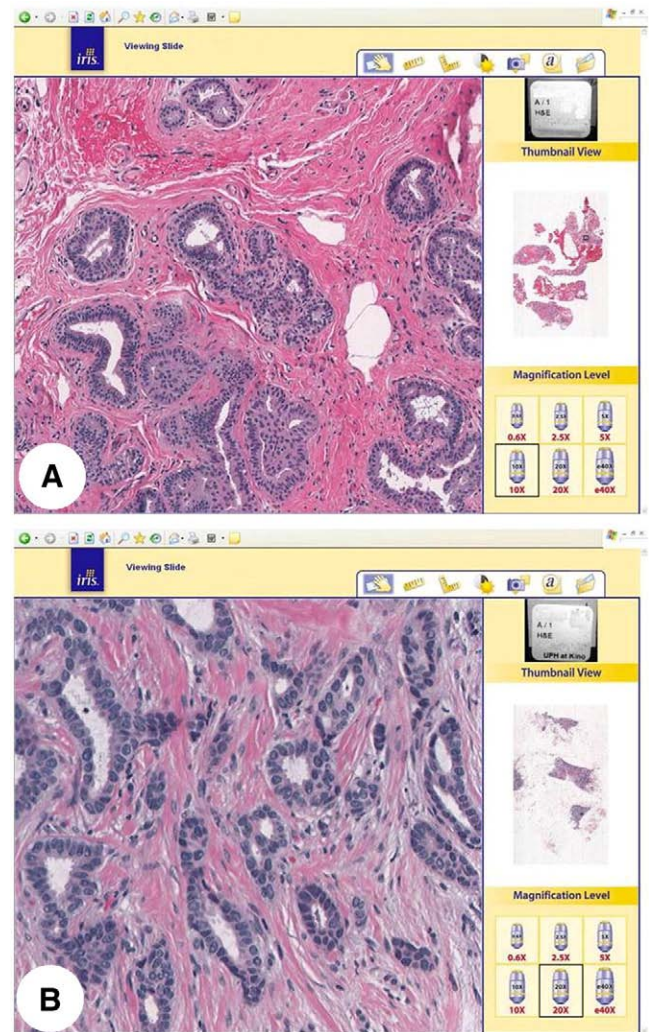


Fig. 3 Photographs of the monitor screen displaying high image quality. (A) Breast hyperplasia (10× magnification). (B) Tubular carcinoma of the breast (20× magnification). In the thumbnail views on the right, a small rectangular cursor indicates the position of the current field being viewed with reference to the tissue sample. Above the thumbnail view is the slide label for the case designation that has been deidentified for this article (DMetrix Iris Virtual Slide Viewer).

breast specimens with 8 hours' neutral buffered formalin fixation and overnight processing.

The first validation study was the comparative study using 25 lumpectomy and mastectomy breast specimens containing previously diagnosed cancer. In these breast marker studies, there was concordance between tissue handled by 30 minutes rapid fixation/rapid processing and that undergoing routine fixation/overnight processing as follows: ER, 100%; PR, 95%; and Ki-67, 90%. Results for the HER-2/neu testing revealed a 72% correlation that is within a numerical range that would not have affected the decision to refer for FISH (fluorescent in situ hybridization) testing (0 versus 1+). Of those cases that represented a disparity of 1+ on one of the specimens and 2+ on the other, only 1 case eventuated in a

Table 1 Comparison of preliminary diagnosis with final diagnosis in cases with major or minor diagnostic discrepancies

Identifier	Preliminary diagnosis	Final diagnosis
Major discrepancy		
1. Breast	Invasive ductal CA	DCIS
3. Breast	DCIS	Ductal hyperplasia
4. Breast	DCIS	Invasive ductal CA
5. Breast	DCIS	Atypical ductal hyperplasia
Minor discrepancy		
13. Breast	Metaplastic CA (adenosquamous)	High-grade CA with medullary features
14. Breast	Florid ductal hyperplasia	Atypical ductal hyperplasia

Abbreviations: CA indicates carcinoma; DCIS, ductal carcinoma in situ.

FISH result of amplification. All 3+ cases sent for FISH were amplified.

The second validation study was based on the 30 (of 32) breast cancer specimens from the telehealth rapid breast care service, for which complete data were available on ER, PR, Ki-67, and HER-2/neu by IHC, and for HER-2/neu by FISH for a subset of cases where this was indicated as established by clinical indications. The institutional policies at both University Medical Center and at University Physicians Healthcare Hospital are to refer IHC 2+ cases for FISH. For these 30 breast cancer cases, all IHC-negative results have been nonamplified and virtually all IHC3+ results have been amplified. The results for ER, PR, and Ki-67 intensity of positivity were virtually interchangeable between the core breast biopsy specimens and the resection specimens, in 95% of cases.

3.3. Virtual slide telepathology quality assurance program

We have analyzed the outcomes of 154 rapid breast care cases, comparing conventional light microscopy pathology diagnoses, on breast core biopsies, rendered by the surgical pathologist on service at University Physicians Healthcare

Hospital, with the quality assurance virtual slide telepathology diagnoses rendered at University Medical Center. For all cases, the surgical pathologist on service at University Physicians Healthcare Hospital always had the option of deferring any single case for a second opinion by light microscopy as is standard practice at the University of Arizona. No pathologist in the University group practice is required to make a diagnosis by virtual slide telepathology although all of them do participate in these programs. Conventional light microscopy is always an option.

There was complete concordance between the quality assurance diagnosis rendered by virtual slide telepathology with the primary diagnosis, rendered by conventional light microscopy in 139 (90.3%) of the breast core biopsy cases. There were 4 (2.3%) major discrepancies that would have resulted in a different therapy and 3 (1.9%) minor discrepancies (Table 1). For all cases in which there were interobserver discrepancies, the final surgical pathology report diagnoses were those generated by staff pathologists at the Quality Assurance Conference. Three virtual slide telepathology cases (1.9%) were deferred for immunohistochemistry, for actin, calponin, or cytokeratins, to establish a primary diagnosis. In 2 breast core biopsy cases (1.3%), the case was deferred for examination of the glass slides by the reviewing pathologists at University Medical Center (Table 2). The cases described in Tables 1 and 2 are a subset of the cases in Graham et al [23].

4. Discussion

Historically, diagnosis and treatment plans for breast cancer were based on a timetable dictated by health care system scheduling, particularly the rate-limiting steps involving physician information and communication with the patient. Much of this was not directly determined by the physician (eg, medical and radiologic scheduling, dissemination of paper-based reports, availability of specialist consultation, among many others). Laboratory testing and reporting also played a role in the inefficiencies of the system. This was in no way unique in medicine. It was simply characteristic of slower, low-tech processes that

Table 2 Cases deferred for additional study using immunohistochemistry testing or for glass slide rereview

ID	Preliminary diagnosis	IHC testing required	Reason for review
Defer to additional testing			
2. Breast	DCIS	Actin and calponin	–
5. Breast	DCIS	Calponin	–
6. Breast	Invasive ductal CA	Cytokeratins and calponin	–
Glass slide review			
7. Breast	Fibroadenoma vs phyllodes tumor	–	R/O adenosis tumor
10. Breast	Pseudoangiomatous hyperplasia	–	Confirmation of diagnosis
12. Breast	DCIS in fibroadenoma	–	R/O atypical ductal hyperplasia in fibroadenoma

Please refer to Table 1 for abbreviations. Abbreviation: R/O, rule-out.

prevailed in general until the latter third of the 20th century. However, the attending physician was central to the information integration.

The communication of results from physician to patient was usually by an in-person follow-up visit with the doctor. Emphasis was placed on a face-to-face encounter between patient and physician, presumably so that the emotional response of a patient with a diagnosis of cancer could be handled by a knowledgeable physician. Direct landline telephonic communication was sometimes used but was not preferred.

Societal norms in the past were also based on a more passive role and a longer time tolerance of the patient toward medical experts' data gathering and decision making. Patient anxiety and emotional distress while waiting for the benign/malignant answer were certainly considered by compassionate physicians, but system limitations would not permit a shortened interval between patient presentation and definitive diagnosis.

Furthermore, the concept that a patient should have control of her body's destiny was not in vogue. During this period, it was not unusual for the patient undergoing a biopsy in the operating room to sign a preoperative release authorizing a radical mastectomy should an intraoperative frozen section sampling be interpreted as breast cancer. Quite literally, a woman could go to sleep not knowing if she would wake up without a breast attached to her chest wall. Similarly, treatment options were limited and defined as rigid, 1-way algorithms, generally without significant patient choice involved. This simply reflected a medical system in which only the personal physician was the designee for treatment decisions.

A variety of different factors contributed to the radical paradigm shift in breast cancer diagnosis and treatment that characterize the late 20th and early 21st century. First—and fundamental—is the exponential progress in technology and telecommunications. Second are the drastic societal changes facilitated in large part by the first factor. A limited sampling of these follows. Access is available by individuals to seemingly limitless information sources through the Internet. Faster and more direct communication is enabled through cell phones, formal and informal computer-based networking, and powerful search engines. A number of Web sites now provide very focused searches on specific topic areas. Third, the public expectations for faster and personalized services dominate the landscape. These factors translate freely into the health care environment.

A host of peer-reviewed publications offer prognostic implications and treatment regimens—in real time—emerging from the above diagnostic criteria and carefully controlled clinical studies [24-26]. Meta-analyses reveal sound, reproducible trends from which additional hypotheses may be explored. Meanwhile, media sources inform the public daily of this information in lay terms, not all of which is positive [27-29].

The new face of breast cancer management is patient-centric and patient-sensitive. Diagnostic elements are being refined with respect to accuracy, speed, and integration with multidisciplinary management plans [8,9]. For example, a typical surgical pathology report in the 1960s would read "infiltrating breast carcinoma" with or without a mention of degree of histologic differentiation. Today, a surgical pathology report of a partial breast resection would include at least 20 components, some of which require quantitative as well as qualitative assessment.

Breast cancer tumor markers, specifically ER, PR, Ki-67 (Mib-1), and HER-2/neu, have become extremely important in clinical practice, both for prognosis and for their predictive value in the selection of the best therapeutic regimens for women with newly diagnosed breast cancer [24-26]. There is a large literature on the value of these markers. More recently, attention has been focused on the potential impact of medical errors derived from faulty breast marker information [27-29]. This negative aspect has included technical and interpretive components, as well as limited expertise of the reporting pathologist [27,28]. Additional studies with multivariate analysis will be necessary to rank order the risk for erroneous results derived from each of the contributing factors.

In the telehealth rapid breast care model, the objective was to minimize the time intervals between initial clinical observations, imaging, needle tissue acquisition, pathology interpretation, clinician/patient discussion, and therapeutic management. Clinical assessment, imaging, and tissue sampling were completed before midmorning. The breast tissue specimen was sent by courier to the laboratory, and accession and gross examination were performed immediately upon receipt. The courier travel time was approximately 15 minutes from the Tucson Breast Center (where the needle biopsies were performed) to the University Medical Center laboratory and 25 minutes from the Tucson Breast Center to the University Physicians Healthcare Hospital laboratory.

Fixation and processing time were reduced using revised, shortened protocols that were previously validated. Sample sectioning and staining were performed as stat procedures, making the slides available for pathologist review by early afternoon. If neoplasm was identified, confirmation of the malignant diagnosis could be obtained through virtual slide telepathology, and the information conveyed to the clinician/oncologist could take place by mid to late afternoon. IHC for breast markers was performed during the afternoon, and those results were available by late afternoon or early the following morning. The communication to the oncologist of the diagnosis occurred by phone or fax before end-of-business the day of the biopsy. The oncologist communicated the laboratory results with the patient the same day as the breast core biopsy.

A variety of scheduling and operational changes were necessary in various services to facilitate the sample delivery to the pathology laboratory no later than late morning.

Thereafter, it was the responsibility of the laboratory for timely handling of the specimen through to diagnosis.

Specimen fixation and processing were the first issues. In the past, formalin fixation occurred for a period of at least 6 to 8 hours before overnight processing. In our validation study from 2005 (performed in compliance with CAP guidelines at that time), it was determined that 30 minutes of fixation of breast tissue, followed by ultrafast tissue processing produced morphologic results indistinguishable from the specimens having a longer fixation and processing period. Similarly, IHC staining intensity for ER, PR, Ki-67, and HER-2/neu did not differ by more than one degree of positivity on a 0 to 3+ scale, except for 2 instances of discrepant Ki-67 results.

The various effects of formalin fixation and tissue processing methods on IHC results have been reported in the past [32-34]. In the early years, formalin-fixed tissue was excluded for use in IHC in favor of fresh-frozen tissue because of concerns regarding antigen preservation. Many of the early observations have been reevaluated for new technology such as microwave and antigen-retrieval methods, with the recognition that fixation and processing procedures may be modified from traditional constructs [32-38]. Particularly relevant is the literature of Ragazzini et al [39] demonstrating that there was no significant difference in IHC results for ER, PR, and Ki-67, between breast tissue samples fixed for 20 minutes in 10% buffered formalin followed by fast processing from samples that were fixed and processed by standard methods. In light of this research and our validation studies for expedited tissue processing, former positions on fixation and processing may warrant reconsideration. As part of this process, it should be remembered that the American Society of Clinical Oncology/CAP consensus recommendations of 2007 were specifically directed toward HER-2/neu laboratory procedures and not necessarily generalizable for other immunohistochemistry testing [19]. For our part, we plan to extend and enlarge our validation studies on HER-2/neu results based on fixation and processing parameters to provide additional objective data for future discussions in this area.

The next issue for speeding up turnaround time to diagnosis was high prioritization of breast needle biopsies at the University Physicians Healthcare Hospital laboratory by the attending pathologist, among the various other surgical pathology duties of the day. This was followed by stat quality assurance protocols for confirmation of newly diagnosed malignancy, based on virtual slide telepathology and carried out by at least one additional pathologist at the University Medical Center laboratory in another part of Tucson.

The final step for the primary pathologist at the University Physicians Healthcare Hospital laboratory was immediate communication to the clinician/oncologist of results through telephone or fax, with a hard copy report—including IHC results if available—generated before the end of the workday. Patient contact with the biopsy results was immediately made by the clinician/oncologist.

Throughout this accelerated diagnostic process, it is critical to ensure that the highest levels of quality control be applied to instrumentation with strict adherence to manufacturers' directions, to reagents (specifically to antigen target with respect to IHC), and to individual laboratories' internal and external quality assurance programs. Similarly, pathologists involved with breast specimen evaluation should be part of a continuous competency assessment plan for surgical pathology. Our virtual slide telepathology quality assurance program (discussed in detail elsewhere in this symposium) revealed a small number of significant diagnostic discrepancies in breast cases that were resolved before finalizing the surgical pathology report (Graham article in symposium). The capabilities of virtual slide telepathology in this context increased the job satisfaction of subspecialty pathologists without special training in breast pathology but assigned to cover the general surgical pathology service at our small satellite university hospital. Preparation by a pathologist for his/her portion of an interdisciplinary breast cancer conference should be an opportunity for "look back" review of prior diagnostic conclusions. The ability to compare findings in sequential specimens is invaluable, especially for breast cancer patients. This process is facilitated by the same laboratory providing services for both outpatient and inpatient tissue handling, which should be vigorously encouraged by surgical pathologists.

Today, the fragmentation of breast care services is part of a systems problem. Many medical practices are mandated (eg, by Medicaid) to send subsets of patients' laboratory specimens to reference laboratories in other cities or states, often without the knowledge of the patient. For example in our institution, for those patients covered by Arizona Health Care Cost Containment System (the Arizona Medicaid equivalent), biopsy specimens from certain clinics are routinely sent to a reference laboratory in another city because of health plan contractual arrangements. Because turnaround times are variable with a number of decentralized laboratories feeding results to clinicians, comparison of biopsy material with resection tissue can be hindered. In this real-world setting, breast care specialists may need to schedule patients for follow-up clinical visits according to a worst-case scenario to be assured that all test material be complete in the patient's chart before the follow-up appointment with the patient. Although breast laboratory testing can be completed in one 24-hour cycle, as discussed in this article, an inconvenient and unfair truth is that certain health professionals will lay the blame for any perceived delay at the laboratory's door.

With regard to the communication of laboratory results to patients, it was anticipated that patients would prefer the face-to-face meeting dialogue that was the traditional method of physician-patient contact in the past. This could be expanded to include simultaneous participation by other breast cancer treatment personnel such as surgeons, radiation oncologists, and other care providers. It was therefore

interesting to discover that telehealth rapid breast care patients preferred telephone (including cell phone) contact by the clinician/oncologist to apprise them of the diagnostic results immediately. It should probably not be surprising that patients expressed this choice in view of the psychic discomfort of uncertainty.

There is a widespread perception by care providers that breast biopsy patients feel intense anxiety in the interval between specimen acquisition and the definitive “answer” of benign or malignant. More recently, that subjective perception of patient anxiety has been supported by objective biochemical findings. Lang et al [40] measured salivary gland cortisol concentrations, which are highly correlated with free plasma cortisol levels, throughout the days in the interval between breast biopsy and the communication of the diagnosis. The cortisol secretion curve “slope” was distinctly flattened (compared to normal) for women in this waiting interval irrespective of whether they would eventually be informed of benign or malignant disease. Furthermore, this slope profile awaiting biopsy results was essentially identical to that of patients after they were told of a malignant tissue diagnosis. The sustained flattening after the diagnosis of cancer was communicated may possibly be due to another period of uncertainty about their future experienced by those for whom the cancer diagnosis was confirmed. In contrast, the cortisol slope for women informed of a benign diagnosis was steeper and closer to normal after receiving the laboratory findings.

A similar phenomenon of abnormal cortisol levels was observed in men in the 2-week interval between prostate needle biopsy and communication of the diagnosis [41]. The patients’ subjective reporting of their psychologic experience likened it to a “nightmare.” Outside the medical sphere, another example of an altered cortisol slope pattern was reported by soldiers shortly after a land mine accident [42]. The cortisol slope had normalized 9 months later. Now, women waiting for breast biopsy results may regrettably add to the list of “chemically stressed” individuals.

There are several implications associated with dysregulated adrenocorticoid levels. One is amplified production of cytokines that promote inflammation and inhibit wound healing [43]. This is of particular interest recognizing that most breast cancer patients will undergo further surgical intervention after the initial needle biopsy. The second is depression of immune function [44] especially significant in patients who—by virtue of chemotherapy—contend with increased risk of infection. Finally, cortisol pattern abnormalities have been linked to progression of malignancy [45]. In light of these observations, an additional compelling need has become apparent for fast-tracking the diagnostic process.

Traditionally, resection tissue was considered to be superior to that of the needle breast biopsy, principally because a larger volume of tumor promised more abundant tumor for study. Today, with the diversity of breast cancer decision options, the needle biopsy may be the only tissue obtained. Some of these decision options follow. The patient

may refuse additional surgery beyond the biopsy procedure. The tumor may be quite small and little may remain after a multiple pass needle sampling. In some circumstances, radiation therapy may be chosen over resection. In these and other situations, postbiopsy hormonal and/or chemotherapy treatment must rely on the information gained from the needle biopsy.

The potential benefit of neoadjuvant therapy for breast cancer has resulted in its increased use for stage 2 or higher tumors. The neoadjuvant approach provides a biological model to guide treatment decisions with a real-time response to cancer chemotherapy that allows for a treatment change, if the initial therapy proves ineffective. This approach was successfully demonstrated in the Aberdeen study (AE), where patients unresponsive to anthracycline-based neoadjuvant therapy were able to achieve a response when treatment was switched to docetaxel [46]. For neoadjuvant therapy, therapeutic decisions are made on biopsy tissue, as it is hypothesized that exposure to chemotherapy may alter prognostic and therapeutic indicators. Although markers are still evaluated on the definitive resection tissue, in cases of pathologic complete response, no tissue is available for marker assessment, and in cases of pathologic partial response, tissue results are interpreted cautiously because the chemotherapy may have changed the marker profile. Given the increasing application of neoadjuvant therapy, the clinical importance of breast needle biopsy tissue grows.

At our institution, pathologists are an integral part of the breast cancer service. As such, we believe that the pathologist is ideally positioned to maximize the potential for expeditious breast cancer management, within the laboratory itself and adjunctive to other care providers. Multidisciplinary cooperation focused on the priority of meeting the patient’s needs is key to such a service.

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