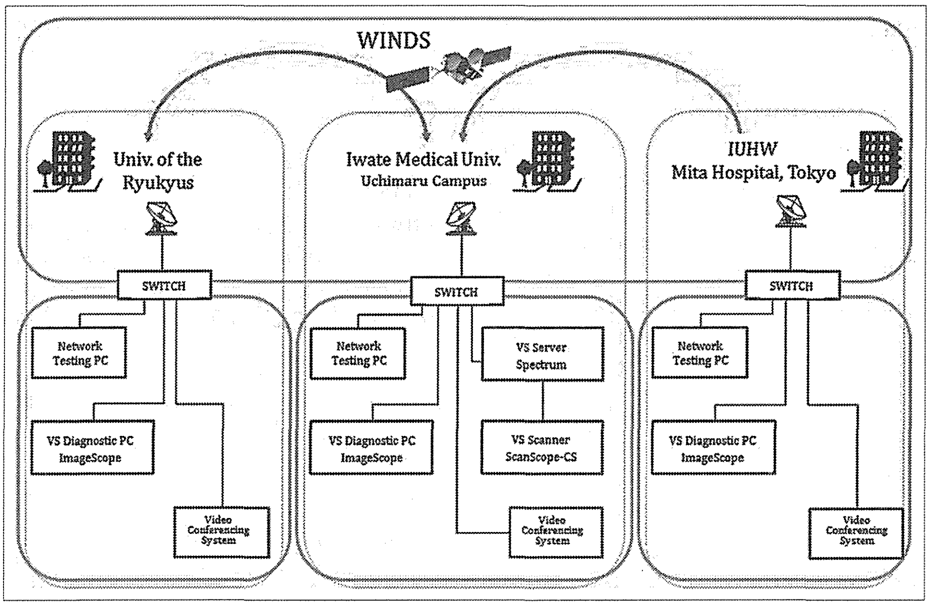

**Figure 2a: Network diagram. Earth stations were placed in the three participating institutions in (Iwate Medical University, Iwate; IUHW Mita Hospital, Tokyo; University of the Ryukyus, Okinawa). Additionally, a scanner and server were placed at IMU. IUHW Mita Hospital and the University of the Ryukyus acted as client institutions and IMU as the consulting hospital**

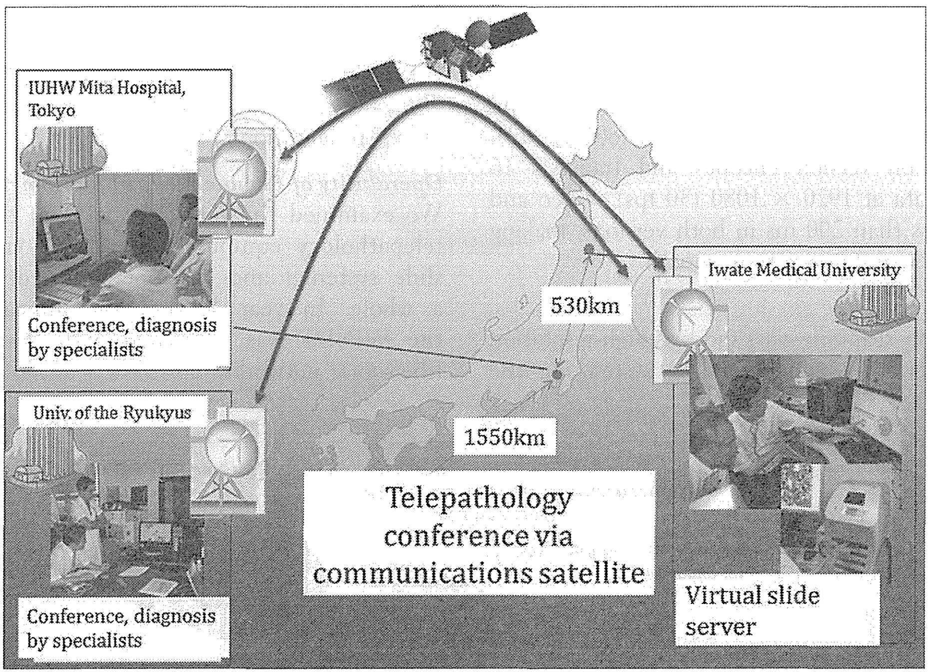

**Figure 2b: Conferencing. Using virtual slides stored in the IMU server and a teleconferencing system, we had a pathological conference between Iwate Medical University, Iwate; IUHW Mita Hospital, Tokyo; and the University of the Ryukyus, Okinawa**

### *Remote Image Diagnosis*

The cases used in our experiments are illustrated in Tables 1 and 2. In year 1, we examined whether or not *Helicobacter pylori* (*H. pylori*) were identifiable with both standard and high-definition images. In year 2, three-way conferencing was tested between institutions in Iwate, Tokyo, and Okinawa. Each location was given control in turn, and 10 cases with significant treatment implications were examined. These cases included cytodiagnosis, a bone marrow smear, HER2 protein expression in breast cancer, and others of interest in targeted therapy.

**Table 1: Year 1 cases**

| Procedure | Clinical diagnosis | Purpose |
|---|---|---|
| Gastric biopsy, H and E stain | Gastritis | Diagnosis and determination of histological characteristics |
| Gastric biopsy, Giemsa stain | Gastritis | Diagnosis and confirmation of *H. pylori* infection |
| Gastric biopsy, H and E stain | Gastric polyp | Diagnosis, confirmation of histological characteristics |
| Colon biopsy, H and E stain | Colitis | Diagnosis, confirmation of histological characteristics |
| Colon biopsy, H and E stain | Colon cancer | Diagnosis, histological typing |
| Lung biopsy, H and E stain | Lung cancer | Diagnosis, histological typing for therapeutic implications |
| Stomach biopsy, H and E stain | Stomach cancer | Diagnosis, histological typing |
| Rectal biopsy, H and E stain | Rectal cancer | Diagnosis, histological typing |
| Rectal surgical material, IHC (CEA) | Rectal cancer | CEA expression, and IHC confirmation of positive area |

H and E: Hematoxylin and eosin, IHC: immunohistochemistry, CEA: carcinoembryonic antigen. Pulmonary and gastric tissue: Histological differentiation of pulmonary tissue made in relation with treatment. H. pylori: H. pylori positively identified. High-definition telepathological images were used because H. pylori is difficult to identify at standard resolution. Colon cancer immunostaining: Stainability of cancerous and non-cancerous areas of a single specimen was compared using carcinoembryonic antigen (CEA) to discriminate tumor and none tumor

**Table 2: Year 2 three-way conferencing**

| Subject | Context/content | Purpose | Therapeutic implications |
|---|---|---|---|
| Lung surgical material H and E | Frozen section | Quick diagnosis classification of lung cancer | Determination for surgical procedure |
| Esophagus surgical material H and E | Frozen section | Quick diagnosis tumor residue in surgical margin | Determination for further excision |
| Thyroid gland surgical biopsy H and E | Parfaffin section | Cancer or not from nuclear properties | Selection of treatment |
| Bone marrow smear Giemsa | Blood smear | Nucleus/cytoplasmic features associated with leukemia | Selection therapeutic procedure |
| Lung cytological diagnosis papanicolau | Cytological specimen | Malignant or not cytoplasm and nuclei | Determination for therapy |
| Breast biopsy H and E | Paraffin section | Difficult case Intraductal or extraductal invasion | Selection for surgical therapy |
| Mammary gland surgical biopsy H and E | Paraffin section IHC (HER2) | Score of HER2 protein, for therapy | Determination of hormonal therapy |
| Skin biopsy H and E | Paraffin section IHC (Ki-67) | Number of Ki-67, proliferative marker for malignancy | Selection for therapy high |
| Lymph node biopsy H and E, IHC | Paraffin section IHC | Monoclonality of lymphocytic tumor | Selection of therapy as plasmacytoma |
| Lymph node biopsy H and E | Consultation of lymph node granuloma | Classification of granuloma | Selection of therapy against tuberculosis |

We examined 10 cases requiring histo- and cytodiagnosis. The specimens tested included tissue from the surgical margin (1, 2), difficult conventional histological diagnosis (3, 6, 10), a bone marrow smear (4), cytological diagnosis (5), and therapeutic uses of IHC (7, 8, 9). Samples included systemic organs; staining and evaluation procedures and treatment options vary by case

## RESULTS

### Communication Network

#### *Communication Quality*

We used standard network testing tools (ping and Iperf) to evaluate communication quality using the WINDS. As shown in Table 3, round-trip time (RTT) averaged 780 ms during year 1 and 800 ms in year 2. These values are in the expected normal range for the WINDS communication network. Iperf measurements of bitrate, loss, and jitter indicated normal communication quality [Table 4].

#### *Maximum Speed*

As shown in Table 5, in year 1, Iperf measured maximum data transmission rate (without application equipment attached) at 38.3 Mbps. In year 2, maximum speed was measured at 19.1 Mbps in all legs of the Iwate-Tokyo-Okinawa three-way conferencing.

#### *Comparison with Fiber-Optic Network*

As shown in Table 6, the data loss rate for communications on fiber-optic landlines was measured at a stable 0%. The WINDS experienced negligible packet loss, and error correction ensured minimal frame dropping. The WINDS achieved stable video transmission of 16 Mbps at roughly 30 fps. Video and audio packet jitter was significantly greater using the WINDS than the fiber-optic connection, but was found to be within normal values for its application mode.

**Table 3: RTT measured with ping**

| | Sender→Receiver | Minimum | Mean | Maximum |
|---|---|---|---|---|
| Year 1 2010.1.27 | | | | |
| 1 hop | Uchimaru→Yahaba | 740.471 | 781.413 | 819.152 |
| | Yahaba→Uchimaru | 740.807 | 779.588 | 818.951 |
| Year 2 2011.6.30 | | | | |
| 1 hop | Iwate→Tokyo | 746.813 | 786.608 | 825.848 |
| | Tokyo→Iwate | 756.958 | 794.970 | 836.155 |
| | Iwate→Okinawa | 746.982 | 785.855 | 824.997 |
| | Okinawa→Iwate | 775.997 | 811.766 | 854.027 |
| 2 hop | Tokyo→Okinawa | 1576.921 | 1604.343 | 1625.646 |
| | Okinawa→Tokyo | 1535.765 | 1572.741 | 1614.639 |

ping: A network administration utility to test host reachability and measure RTT. RTT: Round-trip transmission time between the origin and terminal points of a signal, in this case between the satellite and earth stations. Hop: An excursion from one earth station to another via a communications satellite. 1 hop: Earth Station A → satellite → Earth station B. 2 hops: Earth station A → satellite → earth-based relay station → satellite → Earth station B

**Table 4: Iperf results**

| | Client→Server | Bitrate (Mbps) | Time (s) | Loss | Jitter (ms) |
|---|---|---|---|---|---|
| Year 1 | Uchimaru→Yahaba | 29 | 60.0 | 0 | 0.604 |
| 2010.1.27 | Yahaba→Uchimaru | 29 | 60.0 | 0 | 14.253 |
| Year 2 | Iwate→Tokyo | 14 | 60.2 | 0 | 15.621 |
| 2011.6.30 | Tokyo→Iwate | 14 | 60.3 | 0 | 18.354 |
| | Iwate→Okinawa | 14 | 60.0 | 0 | 1.210 |
| | Okinawa→Iwate | 14 | 60.2 | 0 | 15.959 |

Iperf: A network testing tool with parameters adjustable to measure packet transmission rates, bandwidth, etc. Loss: Packet loss (%) measured by Iperf. Jitter: Data transmission latency (delay) variation

**Table 5: Maximum measured transfer speeds**

| | Client→Server | Bitrate (Mbps) | Time (s) | Loss |
|---|---|---|---|---|
| Year 1 | Uchimaru→Yahaba | 38.3 | 60.0 | 0 |
| 2010.1.27 | Yahaba→Uchimaru | 38.3 | 60.0 | 0 |
| Year 2 | Iwate→Tokyo | 19.1 | 61.2 | 0 |
| 2011.6.30 | Tokyo→Iwate | 19.1 | 61.2 | 0 |
| Max. transmission rate: 19.5 Mbps | Iwate→Okinawa | 19.1 | 60.7 | 0 |
| | Okinawa→Iwate | 19.1 | 61.2 | 0 |

The maximum transmission speed of the WINDS communication network system is the nominal 155 Mbps. However, the earth station used in this experiment was limited to 51 Mbps. In this case, the effective rate was about 38 Mbps (about 70% of the nominal rate). Year 1 connected client and diagnostic facilities directly; the effective transmission rate was 38 Mbps. Year 2 connected client and diagnostic facilities through Tokyo, halving the effective transmission rate

**Table 6: Comparison of the WINDS with fiber-optic network**

| | WINDS | | Fiber-optic landline | |
|---|---|---|---|---|
| | Yahaba→Uchimaru | Uchimaru→Yahaba | Tokyo→Okinawa | Okinawa→Tokyo |
| Transmission rate (kbps) | 16043 | 16021 | 1675 | 929 |
| RTT (ms) | 821.78 | | 43.16 | |
| Loss (%) | 0.334 | 0.42 | 0 | 0 |
| Video packet jitter (ms) | 14.87 | 14.42 | 1.71 | 0.95 |
| Audio packet jitter (ms) | 14.7 | 13.65 | 1.62 | 0.87 |
| Measurement time (s) | 46 | | 428 | |

The above data was calculated from packets captured by logging tools installed in the client computers at each transmission terminus. In application mode, the WINDS uses WarpVision HD (full high definition = 1920×1080) while the fiber-optic network uses WarpVision (QVGA = 320×240). The transmission rate disparity reflects the resolution differences

## Operability of Remote Medical Equipment

### *WarpVision Real-time Video System (Year 1)*

For diagnosis to be made, remote microscopy requires manipulability of the field of vision, zoom, and focus. Overall, the functionality of high-definition image manipulation presented no significant difficulty and was comparable to that with a fiber-optic connection, though the focus lagged approximately 0.8 s.

### *Virtual Slides (Year 2)*

We accessed the Spectrum digital slide management server and confirmed that virtual slides were viewable. The virtual slide images were dithered (displayed as a low-resolution mosaic) while loading, and took approximately 1 min to fully load. Once completely loaded and displayed at full resolution, no inconvenience was experienced in adjusting the field of vision or zoom. Additionally; shape, stainability, and some level of microstructure were observable.

## Pathological Image Cases

### *Year 1 Cases*

Gastric Cancer Biopsy

A biopsy containing both undifferentiated carcinoma and normal tissues was compared. Cellular characteristics of the invasive cancer cells with significant atypia were clearly confirmed and diagnosis was possible with no difficulties.

*H. pylori* Confirmation

Identification of *H. pylori* is difficult with standard-definition images, but not with the high-definition images used in these experiments. *H. pylori* were confirmed with both Giemsa and hematoxylin and eosin (HE) staining, as shown in Figure 3.

Colon Cancer Immunostaining

The cancerous area exhibited brownish-red color indicating positive reaction to the antibody, while the noncancerous area was negative.

Lung Tissue

Cancerous and normal cells were easily distinguishable on the basis of histo- and cytological findings such as cytoplasmic anomalies, nuclear atypia, and chromatin coarseness.

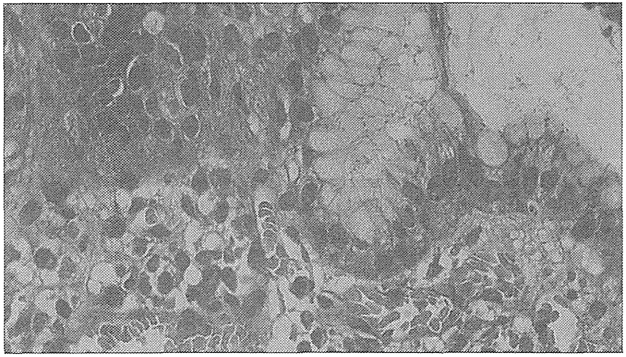

**Figure 3: Giemsa staining *Helicobacter pylori* were visible, with club-shaped figures (25.5 μm in length). *H. pylori* is implicated in the genesis of stomach cancer and malignant lymphoma (arrows)**

### *Year 2 Cases*

We accessed the digital slide server at IMU from two remote points (IUHW Mita Hospital, Tokyo and University of the Ryukyus, Okinawa) and viewed virtual slides. The results of conferencing conducted via the WINDS are summarized below.

Lung Tissue

Tissue sample excised from a lesion from an abnormal chest X-ray shadow. Consultation requested to diagnose and determine treatment. Diagnosis according to Noguchi's classification type A of adenocarcinoma,[16] required focal rather than extended resection lobectomy or radical lymph dissection (lymph adenectomy). (IMU case.)

Esophageal Tissue

Consultation on pathological diagnosis revealed cancer remaining in the marginal region. Additional resection required. No relapse at the time of writing. [Figure 4; IMU case]

Thyroid Tissue

Consultation on malignancy for postoperative histological specimen. Nuclear grooves and inclusion bodies identified, and diagnosed as papillary adenocarcinoma (follicular variant); total thyroidectomy performed with radical dissection of cervical lymph nodes [Figure 5; University of the Ryukyus case].

Bone Marrow Smear

Diagnosis of smeared slide with suspected hemopathies, including leukemia. Images at ×20 magnification insufficient to identify nuclear and cytological characteristics necessary for diagnosis; ×40 images required instead. Diagnosed as benign. (IMU case.)

Pulmonary Cytodiagnosis

Cellular and nuclear characteristics and cellular alignment and overlap are considered diagnostic indicators of

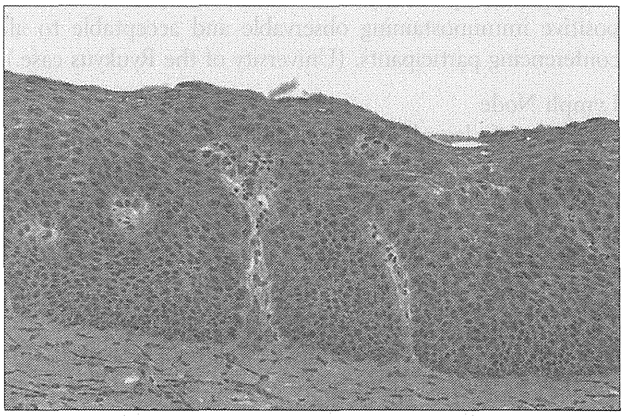

**Figure 4: Esophageal tissue specimen. Additional excision was performed for esophageal carcinoma because of atypical cell residue on the surgical margin**

malignancy. Cytodiagnosis is methodologically simpler than histodiagnosis. This case diagnosed as pulmonary adenocarcinoma based on nuclear atypia and size variation, increased chromatin levels, and cellular overlap. The ×20 images were diagnostically sufficient. However, cytodiagnosis found to require rapid focus adjustment [Figure 6; IMU case].

Mammary Gland
Difficult case of suspected invasive breast cancer. Primarily intraductal, but slight extraductal invasion confirmed. Only local tumor resection and close follow-up required (IUHW case.)

Mammary Gland
Scoring of immunohistochemical HER2 reactivity for selecting antibody therapy [Figure 7]. Recently, targeted antibody therapy has joined the regimen of resection and chemotherapy. Immunohistochemistry (IHC) is used for scoring the amount of HER2 protein, and selecting appropriate treatment. Three samples were immunostained and scored at each facility. All diagnoses matched; two were categorized as score 3, and one as score 2. This sample was referred for fluorescence *in situ* hybridization (FISH). (IUHW case.)

Skin Biopsy
Suspected benign dermatofibroma of the forearm. However, cellular density and nuclear characteristics indicated possible malignancy. Sample immunostained with cellular proliferation marker ki-67. Unable to rule out malignancy despite low ki-67-positive cell count. All three facilities agreed on need for additional immunostaining with CD34 or consultation with dermatopathologist. (IMU case.)

Lymph Node Biopsy
Swelling of lymph node with cell proliferation, characterized by cell shape and nuclear position. Additionally, immunohistochemical staining demonstrated only κ-chain immunoglobulin-positive cell proliferation, led to diagnosis as kappa-type plasmacytoma. Cellular characteristics and positive immunostaining observable and acceptable to all conferencing participants. (University of the Ryukyus case.)

Lymph Node
Swelling of lymph node diagnosed as noncancerous sarcoidosis. Granuloma in this case characterized by little confluence and necrosis. (University of the Ryukyus case.)

## DISCUSSION

The WINDS is one of many Japanese satellites. In addition to communications, satellites are used for weather forecast, disaster prevention, and numerous other purposes in Japan.[17] The WINDS was developed by the Japan Aerospace Exploration Agency (JAXA) and the National Institute of Information and Communications Technology (NICT) in order to overcome the digital divide and provide universal broadband internet service. The satellite is nicknamed "Kizuna" ("connection," or "human bond" in Japanese), a word which has special resonance after the earthquake and tsunami of March

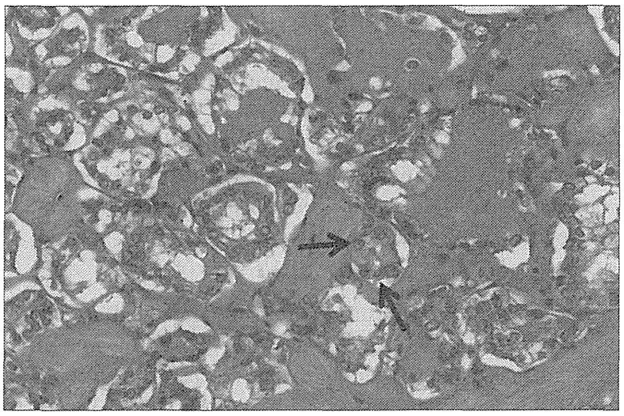

**Figure 5: Thyroid tissue specimen. Thyroid tumor: Diagnosis was papillary carcinoma (follicular variant) with nuclear grooves**

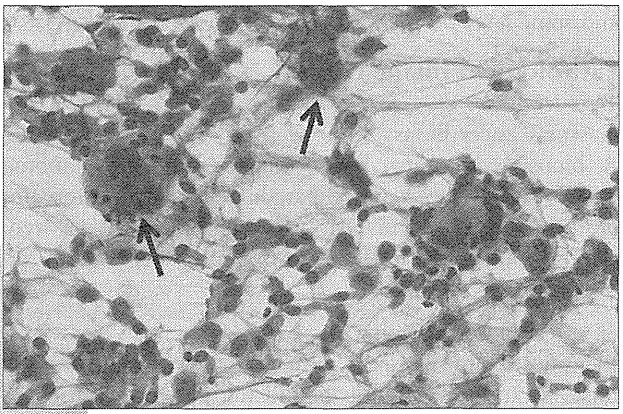

**Figure 6: Pulmonary cytodiagnosis. Cytological diagnosis for sputum: Adenocarcinoma with cluster formation composed of many atypical cells**

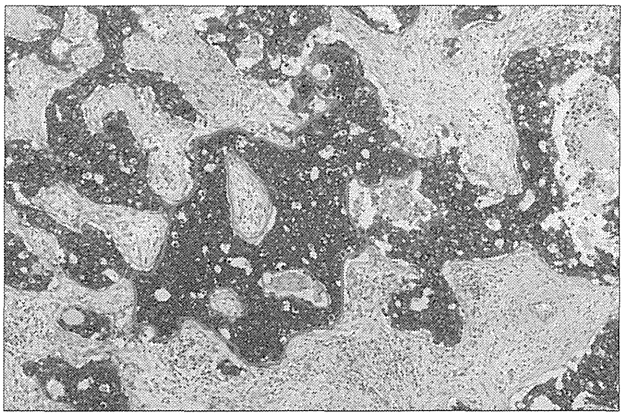

**Figure 7: Mammary gland specimen. The patient received antibody therapy based on the result of immunohistochemical score 2 reactivity for HER2 protein**

11, 2011. The WINDS is still experimental, but potential uses include industrial, scientific and educational services, as well as to provide information for use in disaster prevention. The WINDS is distinguished by a combination of mobility, wide coverage area, and robustness in the event of disaster. It provides higher data transfer speeds using smaller antennas than existing communications satellites. Portable user terminals receive 155 Mbps with 45 cm aperture antennas and transmit 155 Mbps with 1.2 m antennas. Terminals of this size are easily transportable anywhere within the satellite's coverage area. The WINDS has fixed antennas for Japanese and major southeastern Asian cities, and high-speed scanning antennas that provide total coverage of nearly one-third of the globe without reliance on landline infrastructure. This means that if a natural disaster interrupts land-based networks, portable the WINDS terminals can easily be transported into affected areas and easily set up alternative network service. For instance, after the disaster of March 11, 2011, the WINDS mobile earth stations were installed at the Iwate Prefectural Office and the affected coastal cities of Kamaishi and Ofunato, allowing high-definition videoconferencing and internet access.[18] These characteristics mean that, unlike fiber-optic cable networks, the WINDS can provide service in mountainous regions and isolated islands. The WINDS uses an ethernet connection, making it highly compatible with land-based internet networks. The WINDS and landlines can be used complementarily to create more reliable networks. The success of these telepathology experiments indicates that the WINDS interface is well adapted for remote medical services. In the future, it is expected that the WINDS will be used to provide telemedicine services and medical cooperation for the Asia-Pacific region.

Japan has numerous public and private communications satellites in use [Table 7], but the WINDS is capable of data transmission speeds far outstripping any of them. Because telepathology requires the transfer of very large amounts of data, it is highly unlikely that any other available satellite could achieve the image quality and stability necessary for telepathology.

Virtual slides require more preparation (scanning) time than real-time video, but once prepared and saved to a server, they are accessible from anywhere.[19,20] Virtual slides are used around the world in educational settings; according to Weinstein, students at Arizona University use virtual slides exclusively, completely discarding optical microscopy.[1] The Japanese Ministry of Health, Labor, and Welfare (MHLW) has helped fund the purchase of about 250 scanners nationwide for the "standardization of cancer medical services". Throughout the country, 60% of medical schools have introduced virtual slides, and 20% of facilities with virtual slide capability use them in lectures and practice.[21]

WarpScope is a dynamic robotic telepathology system capable of real-time video function.[13] The diagnostic pathologist can select the visual field freely and control the focus of microscope in a user environment almost identical to a traditional optical microscope. Recently, high-definition equipment has been developed. We used high-definition images in WarpScope via WINDS to identify *H. pylori* (2.5-5 μm) bacteria, which are associated with occurrence of gastritis and gastric cancer.

In the first year of this series of experiments, we performed pathological diagnosis using a robotic microscope with real-time video. In the second year, we confirmed that three-way conferencing using virtual slides was feasible via a WINDS connection. Network parameters measured with ping and Iperf were normal, but stage movement, zoom, and conversation suffered a lag of approximately 0.8 s. A delay averaging 60-90 s was experienced when initially accessing virtual slides saved to the server. When one participant changed the objective field significantly, there was a delay of 10-15 s before the slide image was reloaded at the other two sites. Jitter using the WINDS network ranged from 0.604 to 14.253 ms. During loading, images were mosaicked. This phenomenon was unusual when using a fiber-optic network, and may have been due to weather conditions.

No direct connection was established between Tokyo and Okinawa for three-way conferencing. Therefore, communication between these two points required two hops (sender-satellite-Iwate-satellite-receiver). As a result, RTT was nearly doubled [Table 3] over single hop connections, resulting in image and voice transmission delays. This is characteristic of communications satellites.

Conferencing was highly successful. We were able to manipulate the images as we conversed, and all participants reached consensus on histopathological findings; including nuclear shape, cellular characteristics, and structure; and immunostaining results. Our results indicate that, for both educational and pathological applications, WINDS could serve as an effective substitute when and where fiber-optic networks are not available. There are many possible uses for the WINDS. We expect that in the future, WINDS will also be used to communicate with foreign facilities. In addition to consulting with hospitals in the United States and Europe, it should be possible to assist with diagnosis, training, and quality control in Southeast Asia.[22] A high-speed broadband satellite like WINDS could service areas unreached or unreachable by fiber-optic networks (mountainous and desert regions, and isolated islands) resulting in tremendous medical advancements for mankind.

## CONCLUSION

These experiments demonstrate that the WINDS ultra-high-speed internet satellite is suitable both for

**Table 7: Japanese communications satellites**

| Satellite (band) | Service (provider) | Domestic users | Fixed/ transportable | Size | Output | Weight | Transfer speed (bps) | Interface |
|---|---|---|---|---|---|---|---|---|
| WINDS (Ka) | Ultra-high-speed internet (JAXA/NICT) | N/A | Fixed/ Transportable (Loan) | 120 cm | 40 wSSPA | 90 kg | 1-155 M | RJ-45 Router and TCP accelerator connection |
| ETS-VIII (S/Ka) | Engineering test satellite (JAXA/NICT) | N/A | Fixed/Mobile (Loan) | 285×374×125 mm<br>28.5×78×174.5 mm | | 8.2 kg<br>300 g | Voice: 5.6 k<br>Data: 32 k<br>Packets: 1024 k<br>Broadcast: 220 k×6 cH | 140 MHz band<br>IF I/O<br>RJ-45<br>Ethernet |
| Thaicom-4 (Ku/Ka) | IPSTAR internet service (IPSTAR Co., Ltd.) | IPSTAR Co., Ltd. | Fixed c. 150,000 yen (+ installation fee) | 120 cm/ 84 cm | 1 w | 20 kg /10 kg | Home: 1 M/512 k<br>Flex: 2 M/1 M<br>Dual: 2 M/2 M<br>Pro: 3 M/1 M<br>Biz: 4 M/2 M | RJ-45 |
| Inmarsat (L) | BGAN (Inmarsat) | KDDI<br>Softbank<br>JSAT Mobile<br>Japan Digicom | Fixed/ Transportable (Car-/ship-mountable) EX500: c. 400,000yen ea. EX700: c. 700,000yen ea. | Explorer500 218×217×52 mm<br>Explorer700 297×339×51 mm | 14 w<br>14 w | 1.5 kg<br>3.2 kg | Voice:<br>ISDN: 64 k<br>Packets: 492 k<br>Streaming: 128-256 k | Ethernet, USB, Bluetooth<br>Ethernet, wireless LAN, USB, Bluetooth |
| N-Star (S) | Widestar II (NTT Docomo) | NTT Docomo | Fixed/ Transportable (Car-/ship-mountable) c. 370,000yen | Flat-panel antenna 197×180×39 mm | 2w | 1.3 kg | Streaming: 8 k<br>Data: (Packets: 384 k)<br>(64 k data: 64 k) | RJ-45 |
| JCSAT (Ku-band) | ExBird (SKY Perfect JSAT) | SKY Perfect JSAT<br>SNET | Fixed/ Transportable c. 480-680,000 yen ea. Rental: 160,000yen | 75 cm | 2 w | | Internet service<br>Premier: 8M/ 1.2 M<br>Standard: 4 M/400 k | RJ-45<br>10/100Base-T (Ethernet) |
| JCSAT (Ku) | PortaLink (SKY Perfect JSAT) | SKY Perfect JSAT | Mobile c. 10 million yen ea. | Flat-panel antenna 744×649×860 mm | 25 WSSPA | 20 kg | 3 M/1.5M<br>6M/1.5M<br>9M/1.5M<br>(HD-capable) | RJ-45<br>10/100Base-T |
| Inmarsat (L) | Isat Phone Pro (Inmarsat) | JSAT Mobile<br>NTT Docomo<br>KDDI<br>Japan Digicom | Mobile phone c. $600 ea. | 54×170×39 mm | | 279 g | Voice:<br>Voicemail:<br>SMS:<br>Data: 2.4 k | Bluetooth 2.0<br>Micro SD<br>Audio socket<br>Antenna port |
| Iridium (L) | Iridium 9555 (Iridium) | KDDI<br>Japan Digicom | Mobile phone c. 250,000 ea. | 30×55×143 mm | 0.57 w | 266 g | Voice:<br>Data: 2.4 k<br>Packets: | miniUSB |
| Thuraya-3 (L) | Thuraya | Softbank (Limited area) | Mobile phone (w/GSM) c. $500 ea. | 53×128×26.5 mm | | 193 g (w/battery) | Voice:<br>IP data: 384 k | Data Cable (UDC) with USB connector |

This table indicates that the data transmission rates achieved by the WINDS are very high in comparison to those of Japanese R and D, engineering, and commercial satellites currently in service

pathological diagnosis with real-time video and for viewing and manipulating still-image virtual slides for conferencing and consultation. These results indicate that in the future, Japan's WINDS could be used internationally for microscopic image diagnosis, education, and research.

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Original Article

# The history of pathology informatics: A global perspective

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## Abstract

Pathology informatics has evolved to varying levels around the world. The history of pathology informatics in different countries is a tale with many dimensions. At first glance, it is the familiar story of individuals solving problems that arise in their clinical practice to enhance efficiency, better manage (e.g., digitize) laboratory information, as well as exploit emerging information technologies. Under the surface, however, lie powerful resource, regulatory, and societal forces that helped shape our discipline into what it is today. In this monograph, for the first time in the history of our discipline, we collectively perform a global review of the field of pathology informatics. In doing so, we illustrate how general far-reaching trends such as the advent of computers, the Internet and digital imaging have affected pathology informatics in the world at large. Major drivers in the field included the need for pathologists to comply with national standards for health information technology and telepathology applications to meet the scarcity of pathology services and trained people in certain countries. Following trials by a multitude of investigators, not all of them successful, it is apparent that innovation alone did not assure the success of many informatics tools and solutions. Common, ongoing barriers to the widespread adoption of informatics devices include poor information technology infrastructure in undeveloped areas, the cost of technology, and regulatory issues. This review offers a deeper understanding of how pathology informatics historically developed and provides insights into what the promising future might hold.

**Key words:** History, pathology informatics, clinical informatics, electronic medical record, laboratory information systems, pathology education

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## INTRODUCTION

"If I have seen further, it is by standing on the shoulders of giants."

- Sir Isaac Newton

The history of pathology informatics is a tale with many dimensions. At first glance, it is the familiar story of individuals solving problems that arise in their clinical practice of medicine. Under the surface, however, lie powerful forces – technical, regulatory, societal and beyond – that have all played their part in molding our discipline into what it is today. In this monograph, we take – perhaps for the first time in the history of our discipline – a truly global perspective of how the field of pathology informatics has evolved. In doing so, several large-scale trends are immediately obvious. For example, the advent of computers, the Internet and digital cameras were major disruptive events that advanced the practice of pathology in many countries. The prevalence of different technologies in different regions was related to both tangible factors (e.g., availability of trained staff and operational costs) and intangible factors (e.g., regulatory concerns). Though pathology informatics was born in the USA and Europe, it is now a truly global discipline; no single country or continent can lay claim to being the sole driver of our discipline's destiny. If we are to be wise stewards of our discipline, it is necessary for us to know where we have been, not only so that we may give our pioneers and discoverers their just recognition, but also so that we can learn from the successes and failures of past decades.

The aim of this collective effort was to record the history of pathology informatics around the world. Pathology informaticists with knowledge about the field, representing virtually all of the continents, were asked to share their experience, literature, publications, archived documents and images, as well as their insights. Their contributions have been collated and divided up in this monograph by continent and presented below in alphabetical order. While an attempt was made by the authors to comprehensively capture all available detail, we acknowledge that there may be voices and events that were missed.

## AFRICA

The history of pathology informatics in Africa is a story of struggle – and in many cases, triumph – against an almost overwhelming lack of infrastructure and resources. Particularly in sub-Saharan Africa, there was, and still remains, an extreme shortage of medical personnel, including pathologists. Even when medical personnel exist they are generally concentrated in the major cities. The tendency for doctors to emigrate – especially from war-torn areas in which they are arguably most needed – worsened this shortage. As a result, pathology services are often scarce and possibly below acceptable standards, especially with regard to the availability of certain laboratory tests (e.g., immunohistochemistry, molecular studies) and specimen processing. For example, in 2007 Uganda had 18 pathologists serving a population of 28 million, Tanzania had 15 pathologists serving a population of 38 million, and Sudan had 51 pathologists (40 of whom work mostly in the capital city of Khartoum) serving a population of 40 million. In Zambia, there is only one pathologist, at the University Teaching Hospital of Lusaka.[1]

It should therefore, come as no surprise that (a) Africa currently represents perhaps the greatest unmet need for pathology services in the world and (b) pathology informatics in Africa has historically focused most heavily on telepathology applications (primarily with European collaborators) to outsource their work and/or seek expert consultation.[2,3] This is especially true in countries like Sudan and South Africa, which have more pathologists as well as relatively advanced telecommunications and Internet services, and as such were positioned to better leverage multiple telepathology efforts with collaborators from other countries.[1-3] A common theme in Africa, as was the case around the world, was the transformational change in medicine that was realized as a result of the introduction of computers, coupled to networking technologies like the Internet, into healthcare.

### Telepathology

In 1991, Heinz Hoenecke of the USA founded the volunteer organization called Pathologists Overseas with the express purpose of setting up and running pathology laboratories for resource-restricted nations in Africa. Emphasis was initially placed on providing pathology services where the need was greatest and on training local medical professionals to become pathologists.[4] Thereafter, when resources become available and technical limitations were overcome, this organization embraced telepathology in several African countries.[5]

In France, a private company named Réseau Internationale de Télémédecine (RESINTEL) was founded in 1992 at the University of Dijon to provide telemedicine services – with a special emphasis on telepathology – to geographically isolated areas of France. The telepathology system and international telecommunications network that it created – collectively known as TRANSPATH – together provided a platform for static telemicroscopy that was originally telephone-based, but quickly moved to Integrated Services Digital Network (ISDN) and satellite communication methods. By 1994, RESINTEL had signed contracts with – and was providing telepathology services for – hospitals in India, the Middle East, Morocco, and several countries in Africa.

Unfortunately, circa 1998 the TRANSPATH network was shut down due to the fact that RESINTEL could not secure funding for continued operation.[6]

In 1997, the Fundamentals of Modern Telemedicine in Africa (FOMTA) project developed regional networks between research centers and universities of many African countries, using up to 256 kbps ISDN connections for the store-and-forward of medical images (including static telemicroscopy) and the remote control of medical instruments. These initial efforts were limited by the lack of high-quality network infrastructure in many of the target nations and by the nascent state of network-capable collaborative editing and publication software stacks at the time, but were nevertheless successful in providing static telepathology services where none had previously existed.[7] By the mid-2000's, FOMTA – and other regional telepathology projects like it – largely migrated to open-architecture telepathology platforms written atop Linux, Apache, MySQL, PHP (LAMP) stacks, of which iPath has been the most successful in Africa (see section: Data Management Platforms).[8]

The first reports of telepathology and teleradiology services in Tunisia date from 1999. These services – primarily between hospitals in Tunis (Institut Pasteur, Hôpital de l'Enfance) and Nice (Hôpital Antoine) and Marseilles (Hôpital de la Timore) in France – focused primarily on cancer diagnoses utilizing static images. Other similar telepathology projects were developed (e.g., between the Farhat Hached Hospital in Sousse, Tunisia and several French cancer centers), which utilized videoconferencing stations for real-time presentation of cases. This was the first appearance of non-static telepathology methods in Africa.[9,10]

The year 2000 was momentous for telepathology in Africa. In Madagascar, the Pathologists Overseas laboratory adapted a commodity digital camera for use with a microscope, pairing it via Universal Serial Bus to a computer for rapid transmission of static photomicrographs over the Internet.[4] In August of that year, Dr. Agostino Faravelli of Associazione Patologi Oltre Frontiera (APOF) travelled with a microscope and a digital camera to Mwanza, Tanzania, where he enabled static telemicroscopy by E-mailing digital photographs as E-mail attachments to colleagues in various institutions in Italy. APOF subsequently established a local presence in Mwanza, which continued experimentation with telepathology methods over a 7-year period before it closed in 2007.[11] The use of static and live telemicroscopy by these pathologists was discussed with a multinational group of participants in a live online videoconference hosted by the Regional Dermatology Training Centre in Moshi, Northern Tanzania.[12]

2001 marked the startup of the Generic Advanced Low-cost trans-European Network Over Satellite (GALENOS) network, a satellite-based telecommunication infrastructure that offered 2 Mbps interfaces to participating clinics. GALENOS eventually covered a total of 14 clinics in Bulgaria, France, Germany, Greece, Italy, and Tunisia; it enabled intraoperative telepathology using a robotic microscope with a video camera and remote control capability.[2] The iPath platform for telepathology gained significant traction during this year, being extensively used by the Eastern Cape Province Department of Health in South Africa[13,14] and the Réseau Afrique Francophone de Télémédecine (RAFT) project (organized by the Geneva University Hospitals) in developing countries in Western Africa. Both of these pathology education projects delivered interactive courses and the ability for tele-consultation utilizing a single common infrastructure. The RAFT project was particularly successful, extending to 17 African countries (Mali [2001], Mauritania [2002], Morocco [2003], Burkina Faso [2004], Sengal [2004], Tunisia [2004], Cameroon [2005], Ivory Coast [2005], Madagascar [2005], Niger [2006], Benin [2006], Burundi [2007], Congo [2007], Algeria [2007], Chad [2008], Guinea [2008], and Rwanda [2008]) as of the time of the writing of this monograph.[2,15,16]

In 2002, apart from reports about the success of the long-running live telemicroscopy projects of Farhat Hached Hospital in Tunisia, other hospitals in this region such as the Aziza Othmana Hospital in Tunis also reported on their telecytology and telehematopathology projects.[10] Also in 2002, the Nkosi Albert Luthuli Central Hospital in Durban, KwaZulu-Natal (South Africa) – the first hospital in Africa designed for truly paperless operation – opened its doors, and has since been a regional champion of enabling telemedicine through the use of radiology and pathology picture archiving and communication system (PACS) systems.[17]

Another two telepathology systems – both of which have experienced enthusiastic growth to the present day – were born in 2003. The first – a pilot project between the Italian Hospital in Cairo, Egypt and the Civico Hospital in Palermo, Italy – utilized both static and video telepathology. This project has expanded to neighboring countries in recent years and is expected to continue operating into at least the near future.[18] The second telepathology system was located in a more bandwidth-limited milieu: The Kijabe Hospital in Kenya. This latter system – which currently provides telepathology services for over 50 mission hospitals throughout Africa – utilizes a microscope camera attached to a computer, permitting static photomicrographs to be E-mailed to international colleagues for consultation and diagnosis confirmation.[19]

2004 saw the advent of robotic microscopes integrating rudimentary whole slide imaging (WSI) technology in

Africa. At the Allada Hospital in Benin, a Nikon Coolscope was utilized in conjunction with a broadband Internet connection to send both digitized (scanned) slides and digital static photomicrographs of selected regions of interest on glass slides to collaborators in Milan, Italy.[20] Later that year, another Nikon Coolscope was installed aboard a non-governmental hospital ship initially based in Cotonou, Benin, also for static and live telepathology applications. An onboard satellite communication system provided Internet connectivity for this system, which is still in operation in its original configuration today.[21,22] In that same year in Casablanca, Morocco, a telemedicine unit equipped with a satellite connection and four ISDN lines was deployed, utilizing a microscope with an attached digital camera for telepathology.[23] Ethiopia also made large strides in telepathology in 2004, launching a project that connected 10 regional hospitals in the country with the Tikur Anbessa Hospital and the Faculty of Medicine of Addis Ababa University. In the same timeframe, the "Ethiopia Pathology" group in iPath was organized for the purpose of providing second opinion consultations with pathologists from Switzerland and Germany. Moreover, this work has improved access to continuing education and training, raised the level of access to care and drastically reduced the waiting time and cost associated with long-distance travel by patients for diagnosis in that country.[2,24]

In 2005, APOF installed a Nikon Coolscope at the Mtendere Mission Hospital in Chirundu, Zambia, leveraging pre-existing satellite Internet connectivity and Skype (a commercial voice-over-IP videoconferencing application) to allow APOF pathologists (living in Italy) to easily provide telepathology services. This system remains popular in the present day, and has made the Mtendere Mission Hospital the definitive regional hub for pathology services within a 100 km radius.[11] Also in 2005, the Euro-Mediterranean Internet-Satellite Platform for Health, Medical Education and Research (EMISPHER) went live, providing real-time online telemedicine services with high emphasis on network quality of service to most of the countries in the Mediterranean region, including Morocco, Algeria, Tunisia, Egypt, Cyprus, Turkey, Greece, Italy, France, and Germany. EMISPHER integrates satellite Internet connectivity known as MEDSKY (up to 2 Mbps) and a custom real-time telemedicine and telepathology application known as WinVicos. It still remains considerably popular, especially in geographically isolated regions where traditional wired Internet connections may not be possible.[2]

The year 2006 marked the first appearance of modern WSI scanners in Africa. During 2006, the Euro-Mediterranean Network for Genetic Services (MedGeNet) – a European Union funded project – installed an Aperio ScanScope GL at the Hospital Charles Nicolle in Tunisia, and then used that WSI scanner to successfully validate the first ever WSI-based telepathology service in the Mediterranean region.[25] One year later, in 2007, APOF built on their already-successful efforts at the Mtendere Mission Hospital in Chirundu, Zambia, with the installation of an Aperio ScanScope CS. Digitized whole slides were stored on a local File transfer protocol server that was made accessible to Italian collaborators via the pre-existing satellite Internet connection, which had been substantially upgraded to provide sufficient bandwidth to support the upload and download of large WSI files.[11] Two pathologists, located in Italy, independently examined the scanned WSIs remotely.[26]

Of note, 2007 proved to be a landmark year for telepathology throughout the rest of Africa as well. The Africa Teledermatology Project (http://africa.telederm.org/) – which provides dermatology support to local providers throughout Africa (Uganda, Botswana, Malawi, Swaziland, Burkina Faso, and Lesotho) – began operations during this year, utilizing a platform (telederm.org) that was initially only capable of static digital gross photographs and photomicrographs. The main limitations at this time were the number and quality of images available to the remote consultant and their reliance on the referring provider, who usually lacked dermatopathology training, to provide representative photomicrographs.[17] In May 2007, a histology laboratory was created at St. Joseph's Mission Hospital Peramiho in Tanzania, but without a local practicing pathologist. iPath was therefore, used to enable telepathology at this site, utilizing static digital photomicrography to send images for diagnosis to pathologists based in Germany.[27] Also in 2007, at the Kuluva Hospital in the Arura district of northwest Uganda, a microscope eyepiece mounted Motic camera was utilized in conjunction with a laptop to E-mail static digital photomicrographs to a pathologist in Kampala, Uganda.[28,29] Finally in 2007, at the Kahuzi-Biéga National Park in the eastern Democratic Republic of the Congo, the Centre de Recherches de Sciences Naturelles, with the collaboration of the Spanish government, started a human and veterinary telepathology service utilizing a satellite Internet connection.[30]

In March of 2008, a pilot telepathology service known as Remote Access for Health Professionals was established with the objective of promoting evidence-based medicine in developing countries. An asynchronous static telepathology program was created in collaboration between four hospitals throughout Tanzania and Kenya and the Massachusetts General Hospital (MGH) (Boston, MA, USA) to provide dermatopathology consultation to local pathologists, using skin histopathology images captured by microscope-mounted digital cameras in conjunction with iPath. The authors of this work identified limitations with static telepathology that could as they posited, be overcome with increased training.[31] Later in 2008, an initiative in Ghana to use microscopes with attached digital cameras to allow quick consultations failed due to the lack of adequate bandwidth, as well as the high cost of the required equipment.[2] Finally in 2008, the Indian government initiated a project known as the Pan African e-Network (http://www.panafricanenetwork.com/). The objective of this project was to provide tele-education and telemedicine services (including all necessary medical and computer equipment) to 53 remote hospitals in Africa via satellite (International Telecommunications Satellite Organization (INTELSAT), European Telecommunications Satellite Organization (EUTELSAT), Regional African Satellite Communication Organization (RASCOM)) and fiber optic links to 12 super-specialty hospitals in India.[16]

In 2009, the French association Pathology, Cytologie, Dévelοppement (PCD) installed a telepathology service in Brazzaville, Congo, with the cooperation of the Francophone Digital University.[32] Also in 2009, a Zeiss Mirax Live RT system – a combination robotic microscope and WSI scanner – was installed in the National Health Laboratory in Gaborone, Botswana as part of the Africa Teledermatology Project.[33]

More recent telepathology events in Africa date to 2010. In this year, static telepathology was applied to vaginal cytology at the APOF projects in Zambia, Madagascar, and Tanzania for quality control purposes.[34] Also during this year, the French branch of Alliance Mondiale Contre le Cancer, International Network for Cancer Treatment and Research Programs began development of a telepathology network in sub-Saharan Africa for diagnostic, pedagogic, and research purposes, initially for lymphomas (which has now been expanded to a broad range of diseases). Partners in this endeavor were the French National Cancer Institute INCa, the PCD Association, and the Groupe Franco-Africain d'Oncologie Pediatrique. Pilot centers for telepathology have been established in the Kenyatta National Hospital in Nairobi, Kenya, in Dar-es-Salaam, Tanzania, and in Ile-Ife, Nigeria, with the following objectives:[35]

- Online consultations, using iPath, for subspecialty sign-out
- Online support to improve histologic/cytologic techniques
- Online case discussion and lectures
- Support for preparation of publications

Finally in 2010, phase one of the Pan African e-Network went live in 29 African countries.[16]

***Telepathology in South Africa***

Computers with various applications, some of them specifically designed to support laboratory operations, we increasingly introduced into many pathology laboratories around South Africa. For example, in the pathology laboratory of Mthatha General Hospital, these computers were originally supplied by the University of Transkei (now re-named Walter Sisulu University). This allowed pathologists to develop a database using the DataEase software package, which allowed for limited statistical computations to take place. These statistics were used for cancer registries and research. The first computers networked to the Internet were installed at Mthatha General Hospital's pathology laboratory by the health systems trust project (funded by the Henry J. Keyser Foundation, USA) in 1995. These computers – connected to the Internet via analog modems over ordinary telephone lines with the central dial-in node set in Durban, South Africa – were primarily used for sending and receiving E-mail. E-mail attachments were used to transmit histology images and pathology reports (both anatomic and clinical). Health workers from rural hospitals and clinics around this region of South Africa were able to thereby receive their lab results via E-mail. This dial-up system would see enthusiastic uptake and active use until 1998, at which point it was replaced by a web-based information site with online discussion groups (http://www.healthlink.org.za/).

Later in 1995, these computers – now with dedicated modem-based links between the Department of Pathology of the University of Transkei and the Department of Anatomic Pathology of the Medical University of Southern Africa – were used to send still images (microscopy, X-rays, computed tomography (CTs), ultrasounds) to the Telepathology Services of the Armed Forces Institute of Pathology (AFIP) in Washington DC, USA, via the Internet. At first, only static photomicrographs were sent; later, radiology and dermatology images were sent along with the photomicrographs [Figure 1]. Initially, all files were compressed for send-out using the program ISSA (Med Tech, Zagreb), which was installed at both Mthatha General Hospital and the AFIP. Later on, the AFIP introduced a more user-friendly web-based online attachment system for further ease of use. It should be noted that all cameras used in this project at this time were analog and as such scanning/digitization was

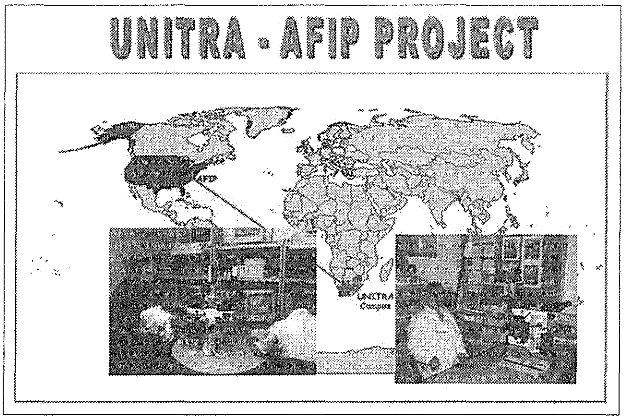

**Figure 1: The telepathology project between the Armed Forces Institute of Pathology (left) and Mthatha General Hospital (right)**

necessary as an intermediate step before the images were sent along to the AFIP. This project would eventually extend into a larger initiative to connect smaller remote hospitals in South Africa and to similarly provide them with remote pathology, cytology, and hematology consultation.[2,36]

The National Committee on Telemedicine and Tele-education was formed in 1998; this committee developed a National Telemedicine Strategic Plan that included several telepathology projects under its umbrella. Phase I of the National Telemedicine Strategic Plan was implemented between March 1999 and September 2000, establishing 28 telemedicine sites in six of the nine provinces of South Africa. Modem-based connectivity was replaced with ISDN (256 kbps) lines, which provided sufficient bandwidth for real-time video conferencing, teleradiology, and telepathology [Figure 2]. Unfortunately, because there was initially relatively low usage of this telemedicine system by pathologists, the software packages used were optimized for teleradiology, not telepathology. As such, the telepathology portions of this system would later migrate to the iPath platform (see section: Data Management Platforms).[14,37,38]

In 1999, a teledermatology project was initiated in Port St. Johns, South Africa, with the aim of improving access to dermatologic care for patients and for the education of family practitioners. In 2002, this project also migrated to the iPath platform. By 2003, this project was connected to a telemedicine network run by the Telemedicine Unit of the University of Transkei in Umtata.[17]

In 2001, as part of an e-health learning initiative, the Free State Department of Health in South Africa set up an interactive satellite broadcasting system that was offered to 40 health and training venues. This initiative extensively utilized iPath for telepathology purposes – with a link between Switzerland, South Africa, and other developing countries – and achieved over 18,000 consultations over the next 4 years. Discussion groups included topics about HIV/AIDS treatment, renal pathology, dermatology, and other topics. This system – which is still in operation today – is now also used to support problem-based e-learning for the medical students at Walter Sisulu University by digitizing exhibits (X-rays, lab results, etc.) and presenting them online.[13,14] 2001 is also significant as it was the year that the National Health Laboratory Service (NHLS) was formed in South Africa, with the purpose of incorporating and electronically connecting all the state laboratories around the country (http://www.nhls.ac.za/). All results from these laboratories are now computerized, stored in a central system, and made electronically available to practitioners around the country.[39]

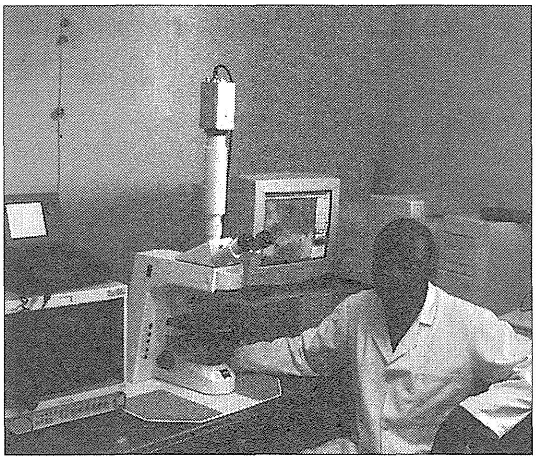

**Figure 2: The South African Telemedicine System at St. Elizabeth Hospital, Lusikisiki**

A mobile pathology laboratory was designed by the South African national Defence Force in 2004, equipped with a remote-controlled Zeiss microscope that could be manipulated via satellite or landline. Operation of this Zeiss microscope is still supported by a dedicated technologist.[40] By 2008, three Nikon Coolscopes had been installed in NHLS laboratories in the cities Mthatha, East London, and Port Elisabeth and connected via local area network (LAN), allowing remote control of the microscopes from any personal computer (PC) on the NHLS network. These laboratories are run by a small number of pathologists, without access to full immunohistochemical studies for some surgical pathology cases, which occasionally makes final diagnosis difficult. This system of Coolscopes is mostly supported by the pathologists located at Stellenbosch University in Cape Town – where it is mostly employed for dermatopathology and oral pathology cases. In 2008, a Zeiss Mirax WSI scanner was installed at the NHLS branch of Mthatha, which is currently utilized primarily for teaching purposes.[39]

## Data Management Platforms

A clinical and research database was used in 1997 to standardize HIV studies in South Africa. This database utilized the systematized nomenclature of medicine (SNOMED) as its coding system and had both client-server and wide area network (WAN) mappings. This system is significant for being the first medical data management system reported in the African medical literature.[41] The implementation and widespread success of iPath servers in Africa, as described in section: Telepathology (Africa) above, provided a powerful platform to manage pathology data in Africa for several reasons:

- Ease of use
- Built atop a LAMP stack using standard, open-source technologies
- Inexpensive (essentially provided for free)
- Minimal hardware requirements

Unlike other areas of the world such as the USA where computing hardware and software is relatively cheap and ubiquitous, in Africa these resources are comparatively scarce (limited vendors) and more expensive. Hence, in this kind of environment, software platforms that are free and that can run efficiently on older hardware – iPath being one example – can flourish. As such, open source software has made significant inroads in Africa; this trend is likely to continue in the future.[42]

### Laboratory Information Systems (LISs)

As section: Telepathology in South Africa indicates, in South Africa, all pathology reports from the NHLS are managed and stored in a central system.[39] Several international data management companies (e.g., Afrosoft International, MEDITECH) also market pathology-centric software packages (e.g., Afrosoft VeriLIMS, MEDITECH LIS) in South Africa.

Many of the LIS installations in sub-Saharan African countries are international projects (usually executed with the help of international non-governmental organizations such as Baobab Health), and are mainly focused on tracking, diagnosing, and defeating common infectious diseases (e.g., AIDS, malaria). This is the case for the Pan-African e-Network,[16] and for collaboration between the University of North Carolina at Chapel Hill and the Malawi Ministry of Health to install a LIS in Malawi.

In many West African countries, pathology services are usually limited to major academic centers and tertiary care hospitals, and LISs are not usually available. Consequently, most pathology reports are still totally paper-based.[43]

### Teaching and Continuing Medical Education (CME)

Medical informatics has been included as a standard part of the undergraduate medical education program in South Africa since 1984.[44] It has kept abreast of technologic innovations, utilizing resources from the country's nationwide telemedicine project and technologies such as WSI scanners as they have become available.[39] In recent years, for instance, telepathology platforms like iPath have been used to facilitate problem-based learning at the University of Transkei/Walter Sisulu University.[38,45] Since 1992, an annual health informatics workshop for various categories of healthcare providers has been held by the Teaching Hospitals Complex and the Computer Sciences Department of Obafemi Awolowo University in Nigeria. This workshop has been a great success, with attendance increasing each year. Workshops like this have been proposed as a model for health informatics training in low-resource countries.[46]

A study at the University of Natal Medical School in South Africa was published in 1996. This study divided students in a histology course into two groups: One was given access to a computer aided instruction package along with standard microscopic learning, and the other was not. Members of the former group spent less time in the regular microscopy lab and showed a slight greater improvement in knowledge relative to students in the latter group.[47] Africa Calls is an annual series of audio teleconferences established by Dr. David Kaminsky in the USA, after he visited South Africa in 1997, with the support of the Annenberg Center for Health Sciences. Since 1999, audio teleconferences broadcast to centers in Botswana, Ghana, Namibia, Nigeria, South Africa, Sudan, Swaziland, Tanzania, Uganda, and Zimbabwe have formed the basis for customized educational programs in cytopathology, including informatics. These programs have been supplemented with downloadable learning material (e.g., PowerPoint slide decks) and other relevant educational material.[2,48] Finally, the first histopathology course in the history of Bulawayo, Zimbabwe was implemented in 2009. This course utilized materials from the local hospital libraries, the Internet, and local clinicians. Response to the inaugural course was enthusiastic, and the course gains more participants every year it is offered.[49]

### Image Analysis

Image analysis papers that stem from Africa are rare. Only a single example could be found. In 1994, the Institut Pasteur de Madagascar in Antananarivo, Madagascar, studied the *in-situ* cellular immune response and associated fibrosis in mucocutaneous leishmaniasis due to *Leishmania braziliensis* utilizing automatic image analytic methods.[50]

## THE AMERICAS

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#### *Canada*

#### *University and Government Infrastructure*

The first few decades of pathology informatics in Canada were dominated by three influential National Health Informatics Organizations. The oldest of these is the Canadian Organization for the Advancement of Computers in Health (COACH). This member-supported organization was founded in 1975 and currently boasts over 1,500 members. As its name suggests, COACH has primarily focused on the use of computer technology in healthcare as well as the effective use of health information for decision-making. COACH holds national conferences and offers a professional certification in health informatics.[51] The second historically significant Canadian organization is the Canadian Institute for Health Information (CIHI). CIHI was founded in 1994 by federal, provincial and territorial governments as a not-for-profit corporation with a mandate that included setting national standards for health information technology and collecting, processing, and maintaining health related databases and registries.[52] The third organization, Canada Health Infoway, is a federally funded corporation created by the Premiers of Canada's provinces in 2001. Since its creation, this organization has been a primary driver of health informatics in Canada, providing partial funding for numerous informatics related initiatives. Although the primary goal of the Canada Health Infoway is to accelerate the development of electronic health records (EHR) across Canada, five of the 193 projects it has funded up to 2011 have focused on LISs.[53] Additionally, the Alberta Netcare portal represents a significant milestone in Canadian pathology informatics. Created in 2003, Netcare is a repository for essentially all laboratory data generated in the province of Alberta as well as for radiology, clinic notes, allergies and medication information. A secure login is available to healthcare providers in the province.[54] More recently, the province of Saskatchewan implemented a similar database, called the eHealth Portal.[55] In the province of British Columbia patients can directly access their own laboratory test results through a secure website called MyeHealth.[56] The province of Alberta has a similar website, part of their myHealth web service, in the planning stages.[57]

*LISs*

Despite the influence of these organizations, many laboratories in Canada were slow to adopt LISs. The first generation systems began to appear in Canadian hospitals in the 1980's, but some anatomic pathology services in smaller communities still relied on type writers and carbon paper as late as 2005. With the exception of a large home-grown LIS in Ontario, Canadian Laboratories have tended to adopt the best North American LIS. Meditech has installations in a number of provinces including British Columbia, Alberta, Ontario and Nova Scotia and is particularly popular in rural and community hospital settings. Cerner has LIS installations in several major Canadian population centers and academic teaching centers as does Sunquest. Sysmex has a large installation in the province of Manitoba. Like the United States, analyzer-LIS interfaces are a mixture of homegrown solutions and vender-supplies middleware. However, increasingly laboratories are moving toward commercial/vender-supplied software to fill this need. Overall, the relatively slow uptake of computer technology in Canadian laboratories may be seen as a reflection of the generally slow adoption of computer technology by Canadian physicians in general. Even in 2012, many primary care physician offices do not use computers at all, much less electronic medical records.

In recent years, there has been an interest in enhancing the functionality of LIS systems to support additional operational and research objectives. A major area of interest in this regard is synoptic reporting for anatomic pathology. In 2012, the non-profit group Canadian Partnership against Cancer with the support of the Canadian Association of Pathologists launched an initiative to implement synoptic reporting across Canada by 2017.[58]

The second area of interest is in using the LIS to assist in utilization management of laboratory tests Predictably, in light of its publically funded health care system, Canada has a long history of interest in utilization management, dating back to 1965.[59] Historically, interest in using the LIS to aid in utilization management has been centered at the University of Ottawa,[60-62] and the University of Edmonton[63] as well as other centers.[64,65] In 2013, the Alberta government established a provincial laboratory utilization office with the intent of using LIS systems in the province to support utilization management initiatives.

*Education and Training Opportunities*

In academic circles, it is only in the past several years that pathology informatics has begun to have a voice in Canada independent of health informatics in general. In July 2009, the Canadian Association of Pathologists added a Special Interest Group in Pathology Informatics. This group has been chaired alternately by Dr. C. Naugler from the University of Calgary and Dr. G. Yousef from the University of Toronto. This group presents a series of short talks each year at the Canadian Association of Pathologists Annual Scientific Meeting. In 2010, the University of Calgary became the first Canadian Institution to offer an official pathology informatics training experience opportunity when it launched a 1 month pathology informatics elective open to laboratory medicine residents. In 2011, the University of Toronto launched a virtual rotation in pathology informatics for the anatomical pathology residents. Currently, academic pathology informatics is centered in three Canadian university departments (Dalhousie University, University of Toronto and the University of Calgary), all of which have academic pathology informatics faculty. However, as of 2013, there are no pathology informatics fellowships available in Canada. A number of other universities have very strong research and teaching programs in bioinformatics including the University of British Columbia and Dalhousie University.

*Telepathology*

The geography of Canada with cities separated by vast distances suggests that telepathology may have a particularly promising future in this country. Despite this, Canada has been relatively slow to embrace telepathology, with the University Health Network in Toronto establishing the first operational system in 2010. This system links several remote northern hospitals to subspecialist pathology support at University Health Network hospitals.[66] It is likely that this model will be repeated in a number of geographically isolated regions in the coming years. Indeed, the necessary infrastructure is gradually accumulating, with whole slide imagers now in routine use for teaching at a number of academic pathology departments. In hematopathology, several large scale installations of the CellaVision system are in use in Nova Scotia, Ontario and Alberta.

In 2011, General electric (GE) Healthcare opened its Pathology Innovation Centre of Excellence as part of the Toronto MaRS Discovery District of technology companies. The facility includes a digital laboratory to facilitate training, research and development on the Omnyx Integrated Digital Pathology platform.

### *The United States of America*

This history of pathology informatics – especially in the USA – resembles a train station from which multiple tracks have emerged and intermittently crossed paths. Historical events are presented chronologically in Figure 3. However, for ease of reading, the history of each area of study within pathology informatics is discussed separately where possible, allowing for the fact that some of these categories have overlap.

#### *Pathology Informatics as a Term and a Medical Subspecialty*

Informatics, including pathology informatics, in the USA began in the early 1950's. The word "Informatik" was first coined in a German publication and likely arose from a combination of "information" and the suffix "-atics," which is derived from Greek and means "the science of".[67] This was shortly followed by use of "informatique" by the French, "informatika" (информатиwка) by the Russians, and finally "informatics" in English-speaking countries including the USA.[67-70] Subsequently, the first definitions of medical informatics as a clinical and research medical subspecialty appeared in the Journal of the American Medical Association (JAMA).[71]

During the same year that clinical informatics was introduced to the medical literature (1990), Dr. Bruce

| 1950s | 1960s | 1970s | 1980s | 1990s | 2000s | 2010s |
|---|---|---|---|---|---|---|
| **1952:** First computers used in clinical labs. | **1962:** CAP establishes the first computer education program for pathologists.<br>**1964:** LINC system described in JAMA.<br>**1965:** Systematized Nomenclature of Pathology published.<br>**1968:** National Committee for Clinical Laboratory Standards (NCCLS) founded. First system for remote pathologic diagnosis demonstrated. | **1970s:** LISs in standard use in clinical labs.<br>**1976:** SNOMED first edition published. First online surgical pathology system in the USA becomes operational at the Massachusetts General Hospital.<br>**1977:** American Blood Commission's Committee for Commonality in Blood Banking Automation recommends adoption of ABC Codabar for blood product labels.<br>**1979:** First regularly scheduled national seminar in pathology informatics (ASCP, twice per year, 1979-1986). | **1980:** First paper describing rotations in pathology informatics for residents is published.<br>**Early 1980s:** First NLM sponsored informatics fellowships are made available.<br>**1983:** First AIMCL meeting.<br>**1984:** *Informatics in Pathology* journal launched. Laboratory Information Systems Division of the AACC formed.<br>**1985:** FDA mandates use of ABC Codabar on all US blood products.<br>**1986:** First telepathology publication. UMLS project begun at the NLM. First calls for pathologists as medical information specialists.<br>**1987:** HL7 is founded with subsequent formation of Laboratory and Anatomic Pathology working groups.<br>**1989:** First book on pathology informatics published. | **1990:** Medical informatics is defined as a medical subspecialty in *JAMA*.<br>**1992:** American Board of Pathology proposes a specialty in informatics to the American Board of Medical Specialties.<br>**1994:** LOINC project is initiated.<br>**1996:** First virtual microscope system developed. First APIII meeting held. NCCLS creates the Area Committee on Automation for creation of standards in laboratory automation including barcoding.<br>**1997:** IHE is formed with subsequent formation of Laboratory and Anatomic Pathology groups.<br>**1998:** ISBT 128 international barcoding standard approved for labeling human transfusion and tissue products. | **2000:** First pathology informatics organization is chartered (API).<br>**2003:** First FDA clearance for quantitative image analysis of immunohistochemical cancer markers. HL7 creates a Genomics Working Group.<br>**2004:** First LabInfoTech Summit. CAP Foundation creates mini-fellowships for pathology informatics.<br>**2005:** Working Group 26 for Pathology is created in DICOM. NCCLS changes its name to CLSI.<br>**2009:** Digital Pathology Association is formed. | **2010:** *Journal of Pathology Informatics* is launched. First combined (APIII + LabInfoTech Summit) Pathology Informatics meeting.<br>**2011:** Clinical informatics becomes official ABMS subspecialty. First nationwide retreat for pathology informatics fellows held in Boston, MA. |

**Figure 3: Major events in the history of pathology informatics in the USA**

Friedman is first credited with using the term "pathology informatics" while concomitantly advocating for the development of separate divisions of pathology informatics within pathology departments. He described the key benefits of having such a division, which included: (i) enhanced productivity and efficiency in application development, (ii) better management of pathology information with oversight by informaticists (also called informaticians), (iii) increased departmental political power, and (iv) increased awareness and sophistication among departmental leaders in information technology.[72] These advantages continue to be true today. Informatics as a recognized subspecialty within pathology was further championed by others who declared that pathology informaticists should play a key role in defining, selecting and implementing all information systems in a pathology department, in addition to being involved in information systems planning for a healthcare enterprise.[73]

Recognition of informatics as a bona fide academic medical subspecialty lagged behind actual practice of informatics (information management) for a time, despite the above efforts. Lack of reimbursement for clinical informatics service likely contributed to limited publication options and research funding as well as recognition from peers.[74] Similarly, clinical wards, outpatient offices and clinics still relied heavily, if not entirely, on paper records, including printouts of laboratory results and reports. This was probably related, in part, to the fact that hospitals were spending an average of only 2% of their budget on information systems.[75] However, as federal legislation surrounding cost accounting, delivery of healthcare and quality laboratory practices began to increase in the late 1980s, including but not limited to the Clinical Laboratory Improvements Act of 1988,[76] more attention was paid to the use of computer systems in healthcare as a whole. Compounded by the promulgation of PCs with graphical user interfaces and the advent of interfaced communications (vide infra), the use of computers in the hospital setting began to skyrocket. As human-computer interactions in medicine began a sharp ascent, the need for physicians to act as medical information specialists (informaticists) was more widely accepted.[71,75,77]

In 1992, the American Board of Pathology (ABP) sent a letter of intent to create an informatics subspecialty to the American Board of Medical Specialties (ABMS). Subsequently, a five-member informatics test committee was convened to write questions for the examination. This effort was unsuccessful at that time for two reasons. Much of informatics involves medical knowledge and complex managerial skills which are difficult to adequately represent in written questions with multiple choice answers, and questions on technical topics were considered insufficient for a clinical informatics board exam.[78] However, beginning in 2009, renewed interest in a board-certifiable subspecialty in clinical informatics spurred the publication of several papers describing criteria for a fellowship in clinical informatics in the Journal of the American Medical Informatics Association.[79-81] In September of 2011, the ABMS announced its approval of clinical informatics as a board-certifiable medial subspecialty. The application was brought forth by the American Board of Preventive Medicine with co-sponsorship by the ABP. This board examination breaks new ground because, unlike most other board examinations which are only open to a few medical specialties, any qualified candidate with primary certification in any ABMS primary specialty may sit for the clinical informatics board examination. Currently, the first examination is anticipated to take place in the fall of 2013. This will hopefully spawn more fellowships in clinical informatics that accredited by the American Council on Graduate Medical Education. At present, however, practicing pathologists may still sit for this board exam under the by-experience pathway, at least for the first five years that the board examination is available.

### *Use of Computers in Laboratories*

Shortly after informatics was defined as a term in the early 1950's, the earliest evidence of data processing in the medical laboratory was reported. Dr. Arthur E. Rappoport presented his experience with the "McBee manual punch card for laboratory data" at the 1952 meeting of the American Society for Clinical Pathology (ASCP).[70] During the next decade, a number of events took place which demonstrated the need for information technology in the laboratory space. At the 1962 meeting of the ASCP, Dr. Rappoport demonstrated the use of IBM punch card systems in the laboratory.[70] In 1964, JAMA published the first article describing a laboratory computer system. This system, called the Laboratory Instrument Computer, was developed by the Massachusetts Institute of Technology.[82,83] Several other early publications in the field, including a monograph, were contributed by Dr. Donald Lindberg.[84-87]

By the 1970's, computer systems were in widespread use in clinical laboratories.[74] Figure 4 illustrates the Spear CLAS-300, an early LIS from circa 1971. The first commercially supported LIS, from a vendor which still today provides such laboratory systems, was implemented at Cape Cod Hospital in 1972 by Meditech. The quantitative nature (i.e., numerical data) of clinical laboratory results and the necessity of performing repetitive calculations helped incentivize laboratories to computerize their processes. These aspects of clinical laboratory data also facilitated automation more quickly than in anatomic pathology laboratories and other areas of healthcare. The first laboratory audio response system – DIVOTS – was developed by Dr. Rappoport at the Youngstown Hospital Association in 1975. CAPER,

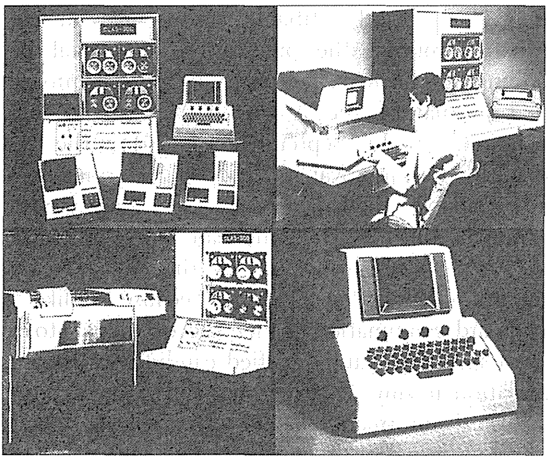

**Figure 4: The CLAS-300. Top left: CLAS-300 with central alphanumeric display keyboard and three remote universal data entry terminals. Top right: data entry on the CLAS-300 (note the large size of the computer components, as well as the magnetic tape-based storage). Bottom left: the CLAS-300's line printer; this particular model, which featured a speed of 300 lines per minute, was considered an incredibly fast printer by 1970's standards. Bottom right: the CLAS-300's central input station; though a large unit, this station was – like the smaller remote data entry terminals: A "dumb" terminal that merely reflected the state of the mainframe that powered it. Photographs reproduced with permission**

the first online surgical pathology information system was implemented in 1976 and served as the inspiration for successive generations of anatomical pathology systems, including Surepath (1978, Tufts), and in 1983 CoPath (descendants of CoPath remain market leaders today). Likewise, the structured textual data used in microbiology proved challenging to implement, but the model created by Peebles and Ryan in 1979 continues to be a crucial component of the Sunquest LIS. Until the late 1980's, information technology in laboratories and other ancillary care areas such as the pharmacy and radiology continued to progress, but most hospital information systems (HIS) were focused on capturing charges rather than the delivery of patient care.[75,77] By contrast, automation, with its concomitant reduction in cost per test, furthered the laboratory's strength as a revenue center for the hospital.[74,75]

*Automated Capture and Exchange of Laboratory Data*

Laboratories enabled with computer technology quickly realized the need to automate transfer of data from the specimen to the instrument to the LIS, and later to the EHR. One of the first aspects of such automated data transfer was realized in the use of barcodes. Concomitantly with the birth of the term informatics and the use of computers in the laboratory, Bernard Silver and Joseph Woodland of Drexel University were granted the first barcoding technology patent in 1952. Adoption of barcodes was initially slow. While the first use of early barcodes in the commercial setting was in 1966, widespread use did not become reality until the mid-1970s.[88] Again, laboratories seemed to be ahead of their medical counterparts in the adoption of new technologies into healthcare. Dr. Arthur Rappoport implemented many creative uses of barcodes in his laboratory in the 1960's and 1970's. While many clinical applications did not utilize barcodes until the 1990s, transfusion medicine made far earlier calls for the use of barcodes for transfused products. In 1977, The American Blood Commission's Committee for Commonality in Blood Banking Automation recommended the adoption of Codabar barcodes for blood product labels. The use of Codabar on blood products was mandated by the United States Food and Drug Administration (FDA) in 1985. In 1994, a new barcode system based on Code 128 symbology was approved by the International Society for Blood Transfusion called ISBT 128.[89] ISBT 128 has been very slowly adopted over the last 17 years as transfusion laboratories are only just now being required to comply with this new standard. By the early 1980's, many laboratory instruments accepted barcode-labeled specimen tubes, and laboratories took advantage of this capability for more rapid, accurate specimen identification as well as automation.

Exchange of data over network lines came later. Health Level 7 (HL7) was formed in 1987 to provide standards for communication of health information between different systems, thereby improving the efficiency of interface implementation and accuracy of data transfer. The formation of several working groups including laboratory, anatomic pathology and genomics took place in the years that followed. In 1997, an organization called Integrating the Healthcare Enterprise (IHE) was formed with subsequent formation of laboratory and anatomic pathology working groups. The overall goal of IHE is to promote the coordinated use of established standards such as HL7 to address specific clinical needs in support of optimal patient care. Just prior to this in 1996, recognition of the importance of automation in the clinical setting increased as the National Committee for Clinical Laboratory Standards (NCCLS) formed an Area Committee on Automation to provide additional technical standards for all aspects of laboratory automated data exchange and workflow including barcoding, interface implementation and robotic lines that move specimens between different instruments for testing.[90-92] In 2005, the NCCLS changed its name to the Clinical and Laboratory Standards Institute (CLSI), to which it is now referred.

Additional discoveries by pathology informaticists furthered automation in several areas. Development of a single system to electronically collect, analyze and manage point-of-care testing data across devices from multiple vendors can be attributed to pathology informatics,[93] and pathology informatics often still leads the way in the implementation of Lean, six sigma, and automation systems for laboratories, resulting in workflow efficiencies and improvements in patient safety.[94-97] Similarly, automated reporting of critical laboratory values with streamlined tracking of communication hand-offs have been generated through the work of pathology informatics.[98]

### *Ontologies, Terminologies and Coding Systems*

Shortly after the advent of computer technology in the laboratory, the College of American Pathologists (CAP) recognized the need to define an ontology surrounding pathology concepts. The systematized nomenclature of pathology (SNOP) was published by the CAP Committee on Nomenclature and Classification under the direction of Dr. Arthur Walls in 1965. Under the long-term leadership of Dr. Roger Cote, SNOP evolved into the SNOMED. The first edition of SNOMED was published in 1976, the 2nd edition in 1979, 3rd (international) edition in 1998, Reference Terminology in 2002 (when Dr. Kent Spackman took up the baton), then following a merger with the British nomenclature Read codes, SNOMED-Clinical Terminology was published in 2004. The CAP with perfect foresight funded and supported the development of SNOMED for almost 30 years. Since then, SNOMED has transitioned to a truly international code, now co-sponsored and funded by 18 countries It is now owned and licensed by the International Health Terminology Standards Development Organization.[99] It is anticipated that the international classification of diseases, 11th revision will be based on SNOMED. It is rewarding to witness how a pathology-inspired terminology initiative has become the world-wide standard for standardized and structured medical terminology.

SNOMED-CT today is the most comprehensive, multilingual clinical healthcare terminology in the world. Dr. Donald Lindberg, a pathologist and informaticist who has been the long-term head of the National Library of Medicine (NLM) started another terminology project called the unified medical language system in 1986 to facilitate the creation of more effective and interoperable biomedical information systems and services, including EHRs.[100] As the availability of automated data exchange grew, so did the scope of that exchange. Laboratories that once only used such technology for transfer of data between the test instrument and the LIS began to expand into the transfer of data between different laboratories. They quickly realized that gaps in the HL7 standard led to challenges associated with transferring test results for the same analyte, but with different methods and reference ranges. Rather than, continue with dependence on idiosyncratic test codes developed in each laboratory independently, the Regenstrief Institute at Indiana University, in cooperation with laboratorians from Utah and the USA and Canada developed a standard coding system for tests and their methods called logical observation identifiers names and codes (LOINC) in 1994.[101] LOINC facilitates the exchange and pooling of results for clinical care, outcomes management, and research and may be used in conjunction with HL7 to ensure correct mapping of test results within a database. Current draft proposals for the Health Insurance Portability and Accountability Act[102] electronic claim attachment standards are based on LOINC codes.[103] Also, the ability to send and receive laboratory results encoded with LOINC codes are an important part of the meaningful use regulations now being implemented by the US Office of the National Coordinator for Health Information Technology.

### *LIS Vendors*

The use of LISs in USA laboratories has depended almost entirely on supply of such software by commercial vendors who install and support these systems. There have been isolated instances of home-grown/self-developed software being used in hospital laboratories, but there have been probably fewer than two dozen long-term survivors. On the other hand, long-term installations of vendor-supported systems have numbered in the thousands.

The history of the LIS is replete with many instances of vendors either going out of business or being absorbed or acquired by other entities. Interestingly, it has been the larger, non-laboratory specific companies that have had the shortest "lifetimes" as LIS providers. Examples include General Electric, International Business Machines, Digital Equipment Corporation, Honeywell, Beckman, Technicon, and Control Data Corporation among others. In contrast, the smaller, laboratory-dedicated firms experienced longer lifetimes, and although often acquired, their LISs were usually continued in use. The USA firm with the longest longevity in the LIS domain is Meditech who installed its first LIS in 1972, and is today still one of the market dominant vendors. Other firms with long, continuous histories as LIS providers include Mckesson, Sunquest (Misys), Cerner (PGI), Computer Programs and Systems Incorporated, Diamond Computing, Comp Pro Med, Psyche (SAC), and Soft Computer Consultants. Of 64 LIS firms in business in 1988, only 15 remain in business today. Over the years, despite competition for a dwindling number of potential customers, new firms have entered the market. As of 2011, 33 companies offer complete LIS solutions. Figure 5 offers a reasonably complete timeline of LIS vendors serving the US market from the late 1960's to the present.

### *Digital Pathology, Telepathology and Image Analysis*

The use of digital images in pathology was a latecomer to the pathology informatics scene. In 1968, analog video-based telepathology was first demonstrated by Ronald Weinstein and colleagues in Boston via a link between Logan International Airport and MGH [Figures 6 and 7]. This showcased the potential