Hyperspectral Digital Imaging (HSDI) Phase IV

Background and Statement of the Problem

The Army's Project AKAMAI is continuing its multi-phase program to develop medical instrumentation and clinical diagnostic techniques that use spectral fluorescence and reflectance imaging. The Hyperspectral Diagnostic Imaging (HSDI) program is dedicated to three areas of medical application:

- Diseases and Disorders of the Uterine Cervix, including Cervical Cancer
- Diseases and Disorders of the Ear, Nose and Throat
- Diseases and Disorders of the Skin (Dermatology)

Review of Phases I – III (FY96-98)

HSDI Phase I was used to determine diagnostic imaging techniques that would non-invasively detect cervical cancer and its precursors. Tasks for this phase comprised research of the literature, protocol planning, development of an experimental instrument (both hardware and analysis software) for *in-vivo* testing, and early determination of spectral discriminators that could be compared with standard clinical histopathology.

A HSDI I prototype was placed at Tripler Army Medical Center (TAMC) in September of 1997. Over 90 women have undergone HSDI cervical scans with this prototype. Data collection and analysis have been ongoing. Preliminary diagnostic discriminators have also been drawn out.

Data collection complied with TAMC standard medical procedures for PAP smear and colposcopic evaluation tissue collection. Spectral analysis has been correlated with both PAP smear analysis results and physician observations during colposcopic examinations. Colposcopic examination results were compared to tissue hispathological evaluations by staff pathologists at TAMC and a second pathologist at the University of Louisville. All biopsies were directed by the colposcopic examination.

HSDI Phase II was used to accomplish three primary objectives:

1. Refine HSDI Cervical Instrumentation
2. Continue Development of Spectral Diagnostic Techniques
3. Begin Planning for Clinical Trials

The HSDI instrument was redesigned to enhance diagnostic sensitivity. Investigation continued on spectral diagnostic techniques. An algorithm was developed for rapid classification and display. TAMC clinical testing was expanded to broaden the database for histopathology comparisons.

HSDI specificity capabilities relative to the differentiation of (1) diseased from non-diseased tissue and (2) high grade from low grade squamous intra-ephitheal lesions (SILs) were also refined.

Efforts were initiated relative to the identification of three additional clinical test sites and respective principal investigators. This effort included the preparation of supplemental applications and an investigation plan for each site, investigator training outlines, and set-up of necessary records and report processes.

HSDI Phase III has continued the development of the HSDI instrument, diagnostic discrimination techniques, data collection and processing. The program was expanded to encompass the three medical application areas of cervical, ENT, and dermatology. A literature search relative to ENT and dermatology studies has been conducted, clinical testing has been continued with the Phase I instrument, data has been collected and processed, and the results evaluated.

Four Phase II cervical instruments, one First Generation ENT instrument, and one First Generation Dermatology instrument are being developed for placement and testing at the selected clinical sites. One Phase II cervical instrument will replace the current Phase I unit at TAMC. Another instrument will be placed at Walter Reed Army Medical Center. The ENT and Dermatology instruments will be placed and phenomenology evaluations initiated at TAMC. As soon as the principal investigator and the HSDI team deem that the units are ready for on site testing, cervical instruments will be placed at Willford Hall U.S. Air Force Medical Center (Lackland AFB, TX) and San Diego Naval Medical Center (Balboa Park, San Diego, CA). This is anticipated to occur at the inception of Phase IV work based upon an expected change in the current Delivery Order.

The additional cervical test sites will enable the expansion of patient and sample populations for *in vivo* examinations. This will help us to better comprehend the HSDI system's effectiveness, sensitivity and specificity.

FY 99 HSDI IV New Tasks and Objectives

HSDI Phase IV is comprised of seven principal tasks.

1. Develop a Next-Generation HSDI Cervical Instrument to include finalization of protocol for FDA clinical trials;
   -Continue performance trials at Tripler and Walter Reed
   –Proceed with FDA clinical trials at TAMC & Walter Reed;
   -Proceed/expand FDA trials at San Diego Naval Hospital and Willford Hall Medical Center.
2. Develop a Next-Generation (Proof of Concept) HSDI ENT Instrument; Continue Clinical Testing at TAMC
3. Develop a Next-Generation (Proof of Concept) HSDI Dermatology Instrument; Continue Clinical Testing at TAMC
4. Development HSDI research as a named area of interest and core competency at TAMC
5. Initiate investigation of patent rights and dual use technology transfer of HSDI instrumentation
6. Provide a Broad Agency Announcement for new applications of HSDI technology
7. Conduct Formal progress Reviews

Each task is discussed, with a comprehensive delineation of actual work to be accomplished, in the following sections.

HSDI Task 1: Develop a Next-Generation (Proof of Concept) HSDI Cervical Instrument; Continue Performance of Clinical Tests

1.1. Continue Clinical Testing at Walter Reed and TAMC
1.2. Initiate Clinical Testing at San Diego Naval and Wilford Hall (San Antonio)
1.3. Perform Statistical Evaluations of Clinical Test Data
1.4. Maintain Clinical Trial Records
1.5. Refine Diagnostic Discriminators
1.6. Develop a Next Generation HSDI Cervical Instrument
    1.6.1. Advanced Technology (Minimal or No Moving Parts)
    1.6.2. Ergonomically Designed; User Friendly
    1.6.3. Real-Time Processing
    1.6.4. Cost Effective
    1.6.5. Enhanced Performance

Clinical tests will continue at Tripler and Walter Reed. Specific attention will be paid to diagnostic discrimination relative to differences in wavelengths. Tests will be initiated at San Diego Naval and Willford Hall. Data will be collected and processed for continued correlation with accepted standard histopathology.

We will comply with all regulatory and IRB requirements regarding the conduct of clinical testing. All regulatory and IRB requirements will be met for testing at San Diego Naval and Willford Hall. Likewise investigation plan protocols will be complied with. Clinical support personnel will be provided help ensure that the instruments are operating properly and in regulatory & IRB compliance.

We will conduct statistical evaluations of the results from all four sites. Methodologies will be based upon the established investigation plans pertaining to conducting the tests and quantifying outcomes. This will include a continuance of comparisons with standard clinical histopathology. Continuing on the process of Phase III, the two quantified outcome factors will be system sensitivity (the systems' capacity to identify the true positive portion of patients having the disease) and specificity (the system's capacity to diagnose, or "rule in", diseases).

We will support the collection and management of HSDI data. Personnel support will be provided for clinical examinations, instrument maintenance, spectral analyses, phenomenology, tissue scanning and analysis, and image processing.

Image processing and spectral discriminator refinement will continue through the analysis of phenomenology and biochemical effects influencing tissue fluorescent signatures. This will enable us to further understand the nature of spectral emissions, apply different analytical techniques, and make instrument enhancements.

Based upon our findings from Phases III and IV, we will develop the next generation (Proof-of-Concept) HSDI cervical instrument. The new instrument will

- Encompass new technology and have minimal or no moving parts
- Be ergonomically designed
- Provide real-time image processing
- Be cost effective
- Provide enhanced diagnostic performance

2.0 HSDI Task 2: Develop a Next-Generation (Proof of Concept) HSDI ENT Instrument; Continue Clinical Testing at TAMC

2.1 Continue Clinical Testing Support at TAMC

2.2 Perform Statistical Evaluations of TAMC Test Data

2.3 Refine Diagnostic Discriminators

2.4 Develop Next Generation (Proof-Of-Concept) HSDI ENT Instrument

2.5 Recruit and Secure Clinical Test Sites and Principal Investigators

2.6 Support ENT Test Protocol and IRB Approval

2.7 Install Units and Begin Clinical Testing

Current difficulties encountered in identification of the presence and type of infection behind the ear's tympanic membrane provides a significant opportunity for the HSDI system. To date diagnosis of infections behind the membrane has been a problem due infection differentiations plus inflamation without infection. The membrane's thickness has also been an issue.

In other areas applicable to the HSDI ENT system, tumors of the pharynx and larynx often go unrecognized in initial presentation. Such delays contribute to poor prognoses of patients with tumors. Most oral cancers are moderately advanced at the time of diagnosis. With regard to bacterial infections, current throat culture and rapid detection methods may be falsely negative in 30% or more of cases.

Early detection of squamous cell carcinoma is key to successful management of dysplasia. The HSDI system, as a pre-emptive screening and diagnosis tool, is expected to facilitate this need. It will further preclude later stage biopsies and therapies of tumors beyond the stage of reversal.

System development and testing will begin with a focus on disorders of the ear. Testing on chinchillas, initiated during Phase III, will be completed. Chinchilla testing will encompass the introduction of inner ear infections followed by fluid extraction for imaging and/or imaging of the inner ear within the animal. Fluorescence and reflectance spectral data will be collected as preliminary evaluation of the HSDI techniques for ear infection diagnoses. Testing and data collection will be coordinated with the TAMC principal investigator.

We will conduct statistical evaluations of the results. The methodology will be based upon the established investigational plan.

Image processing and spectral discriminator refinement will continue through the analysis of phenomenology and biochemical effects influencing tissue fluorescent signatures. This will enable us to further understand the nature of spectral emissions, apply different analytical techniques, and make instrument enhancements.

Based upon test results, a new next - generation (proof-of-Concept) HSDI ENT instrument will be developed.

We will provide support for the development of test protocol. The investigation plan will be in compliance with FDA and IRB requirements. We will support the collection and management of HSDI data. Personnel support will be provided for clinical examinations, instrument maintenance, spectral analyses, phenomenology, tissue scanning and analysis, and image processing.

3.0 HSDI Task 3: Develop a Next-Generation (Proof of Concept) HSDI Dermatology Instrument; Continue Clinical Testing at TAMC

3.1 Continue Testing Support at TAMC
3.2 Produce and Evaluate Clinical Test Data
3.3 Refine Margin Definition Discriminators
3.4 Develop (Proof-Of-Concept) HSDI Dermatology Surgical/Excision Instrument
3.5 Support Test Protocol and IRB Approval

The skin is the most accessible "organ" and clinicians have developed reliable methods to approach and diagnose skin diseases during routine office visits. Differential diagnosis of skin disorders is based upon one prevailing feature: the appearance of morphology of the skin lesion. Physician skill in differentiation is the key. The current American Cancer Society mnemonic "ABCD" (Asymmetry, Border Irregularity, Color Variegation, and Diameter greater than 6 mm) serves as the standard process for clinician examination of suspicious moles. This algorithm, developed at New York University, is not absolute, but generally accepted. Current diagnosis also may include biopsy: shave, punch, or ellipse. The tissue is sometimes used for cultures, but is more often sent for light microscopy, immunofluorescence, electron microscopy, or special staining

The HSDI system is expected to serve effectively as a diagnostic (and eventually a treatment) system. This applies, for example, to imprecise biopsies in that not all of the diseased tissue may be excised at one time. Treatment may thereby encompass repeat surgical excisions that may ultimately include the removal of normal healthy tissue along with the malignant cells due to imprecise localization and delineation. With its prospective capacity for diseased cell localization and capacity to precisely differentiate diseased tissue margins, the HSDI system is expected to eliminate the need for repeat resection.

4.0 Develop HSDI research as a named area of interest and core competency at TAMC

A principal value of the AKAMAI program is its contribution to the economy of Hawaii. The HSDI program presents itself as an opportunity to demonstrably advance this AKAMAI objective.

Because of its role to date, we propose to establish and develop TAMC as a military *Center of Excellence* relative to diseases and disorders of HSDI's areas of medical applications.

We plan for all clinical support to be based in Hawaii. Nation-wide clinical test and trail management will be centralized in Honolulu. Support personnel is planned to encompass HSDI-related employees plus local consultative assistance.

5.0 Initiate investigation of patent rights and dual use technology transfer of HSDI instrumentation

Provide formal evaluation of government and contractor property rights as it pertains to current/existing and future patents on HSDI technology under investigation under this program.

6.0 Provide a Broad Agency Announcement for new applications of HSDI technology

The intent is to broaden our scope of investigation to other potential clinical areas of interest. This investigation will be limited to no more than 25% of the total amount allocated to the HSDI program.

7.0 Conduct Four (4) Formal In-Progress Reviews (One Per Quarter)

We will conduct formal In-Progress Reviews (IPR) quarterly (every three months) beginning with the first IPR three months after receipt of the Phase IV Delivery Order. These IPRs will enable AKAMAI to review progress and to ensure the success of HSDI Phase IV. Draft agendas will be submitted to AKAMAI in advance. Following acceptance by AKAMAI, the approved agenda will then be sent to Review attendees.

IPRs will be in approved presentation format. A copy of the presentation charts will be included in the following monthly report.

HSDI Phase IV Period of Performance

Phase IV is proposed to commence on June 1, 1999 and extend through May 31, 2000.

Performance Objectives / Deliverables

The following will be delivered for HSDI Phase IV.

1) Development of a Next Generation HSDI Cervical Instrument prepared to undergo FDA clinical testing.
2) Clinical Support for all HSDI cervical, ENT, and dermatology instruments installed at test sites
3) A Report of Statistical Evaluations of the data results from the clinical tests for cervical
4) Development of a Next Generation (Proof-Of-Concept) HSDI ENT Instrument
5) A Report of the Results of HSDI ENT Tests including recommended next steps for the program
6) Development of a Next Generation (Proof-Of-Concept) HSDI Dermatology Instrument
7) A Report of the Results of HSDI Dermatology Tests including recommended next steps for the program
8) Investigate new clinical applications of HSDI instrumentation through BAA responses.
9) A TAMC named area of interest/core competency program for HSDI research will be outlined in a strategic plan, pertinent action steps, resource requirements and financials, plus an economic valuation of commercialization of HSDI products.
10) Provide legal review and report of patent and property rights of HSDI instrumentation for the government and associated contractors.
11) Monthly Reports describing program progress and findings to date.
12) Formal In Progress Reviews beginning with the first session three months following receipt of the Phase IV delivery Order
13) A Final Phase IV Report with a draft copy submitted prior to the end of Phase IV and the final copy submitted within thirty (30) days following receipt of customer comments. The report will include the results of the studies and recommendations for HSDI Phase V.