Update on Human Papillomavirus

PART 1

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This is the first in a two-part series designed to discuss the current understanding of human papillomavirus (HPV). This month’s article (part 1) will describe the natural history and pathogenesis of HPV, discuss the relationship between HPV and the development of cervical cancer, and outline the current methods (and limitations) available to detect HPV. The January 2007 article (part 2) will describe the use of HPV DNA testing in managing women with abnormal cytology, and HPV testing as an adjunct to cytology for primary screening. In addition, part 2 will include information on the newly released HPV vaccine and its implications for patient testing and management.

INTRODUCTION

It is now well accepted that infection with high-risk genotypes of HPV is required for the development of invasive cervical cancer. This is based on several lines of evidence: HPV DNA (high-risk types) is found in virtually all invasive cervical cancers; there is a significantly higher risk of developing cervical cancer in women infected with high-risk types of HPV compared to women not infected with high-risk types of HPV; HPV infection has been shown to precede the development of cancer; HPV has been shown to cause transformation of normal cells by integrating its genome into host cell chromosomes. New changes in screening strategies as well as the recent approval of HPV vaccines to prevent infection make it important to understand the biology of HPV as well as how to use HPV diagnostic tests.

VIRUS

Papillomaviruses are heterogeneous, tumor-causing viruses that are widely distributed in nature and are found in many animal species. These viruses are host specific in that viruses that infect one species will not infect another species. Over 120 different genetic types (genotypes) of human papillomaviruses have been identified, with different types...
having a predilection for infecting different tissues. While several types are associated with common hand and plantar warts, approximately 30 are genital types, infecting mucosal epithelium and skin. These genital types are divided into high- and low-risk based on the risk of developing cervical cancer following infection. HPV 16 and 18 are the most common high-risk types associated with cervical cancer, being detected in approximately 70% of the cases. Low-risk types are uncommonly associated with cervical cancer, but are associated with genital warts (condyloma).

### INITIAL INFECTION

A majority of sexually active women acquire infections with genital types of HPV soon after the initiation of sexual activity, and many of these infections are with high-risk types. Current data suggests that while condom use can reduce the risk of acquisition, it does not completely protect individuals from acquiring infections. Since there is a high rate of infections with high-risk types of HPV, it is important to de-stigmatize this so that the focus of patient management is on identifying cancer if present.

### OUTCOME OF INFECTIONS

There are two potential outcomes for women infected with HPV: transient, self-limiting infections, and persistent infections. Transient infections are the most common type of HPV infection. A study in sexually active, HPV-naïve, college-age women showed that 70% of newly infected women cleared their infection within 12 months of acquisition and over 90% cleared within 24 months (1). Transient infections can also cause cytologic abnormalities in the cervical epithelial cells as a result of HPV-induced cytopathic effect. These abnormal cells are called koilocytes and the number and severity of infected cells can result in a diagnosis of low-grade squamous intraepithelial lesion (LSIL) or atypical squamous cells (ASC).

Persistent infections can result in the development of high-grade dysplasias (cervical intraepithelial neoplasia [CIN 2,3] lesions and invasive cervical cancer), but from a molecular virology standpoint, there is no standard to define persistence. Most studies define it as detection of the same HPV type in a patient on more than one occasion. However, this is problematic in practice because the most common test method used combines detection of most of the high-risk types into a panel that does not differentiate among the individual types. Repeated detection of different high-risk types does not confer the same level of risk as repeated detection of the same type. In spite of this, studies examining persistence have shown that at 6 months, approximately 50% of infections are persistent, at 12 months ~30% are persistent, and at 24 months 10-20% are persistent (1-6). While these studies examined persistence in younger women, persistence in women over age 30 happens at a much lower rate, but is more frequent in women infected with high-risk HPV types. Although transient infections can cause minimal cytologic changes, cytologic abnormalities in the context of persistent infections can progress to pre-cancerous lesions, which can ultimately become invasive cancers.

### HPV INFECTION AND THE DEVELOPMENT OF CERVICAL CANCER

Approximately 1/3 of HPV DNA positive women will develop cytologic abnormalities within 5 years of infection, with up to 10% of women infected with high-risk types developing CIN 2,3. Furthermore, women with persistent infections of high-risk HPV types are at the greatest risk for developing CIN 2,3 and cancer. Therefore, the utility of HPV DNA testing is to assist in identifying women who have persistent infections and are at the greatest risk for developing cervical cancer. Additionally, cervical cancer is much less likely to develop in women who become HPV DNA-negative upon follow-up testing.

### METHODS FOR DETECTING HPV DNA

Although in-situ hybridization and polymerase chain reaction (PCR)-based methods exist for the detection of HPV DNA, the only method approved by the U.S. Food and Drug Administration (FDA) for clinical use is the Hybrid Capture® 2 (hc2) HPV DNA assay (Digene Corporation, Gaithersburg, MD). This is a “solution hybridization" method that uses 2 separate pools of
probes to identify either high-risk or low-risk HPV types in a sample. The probes will hybridize to HPV DNA present in the specimen, and the resulting probe:target hybrids are then captured and detected. Many laboratories are routinely testing using only the probes to detect the high-risk types of HPV, as this testing provides the most clinically useful information. A major limitation of the hc2 assay, however, is that the analytical sensitivity of the test is approximately 5,000 copies of HPV/sample, so women who test negative with the high-risk probes may still be infected with high-risk types of HPV. Therefore, the test cannot be used to determine whether or not a woman is infected with HPV, it can only be used as a way of determining a woman’s risk for having high-grade cervical neoplasia.

**HPV DNA TESTING AT MLABS**

MLabs Clinical Microbiology Laboratory is routinely testing with only the high-risk probe set for the hc2 HPV DNA assay. Specimens approved by the FDA for testing in this assay include cervical brush samples collected directly from the cervix and placed in Digene’s specimen transport media, tissue biopsies in Digene transport, and ThinPrep® cervical cytology specimens (Cytyc Corporation, Marlborough, MA). Furthermore, other female urogenital specimens and specimens from males are not approved for testing by this method. However, MLabs Clinical Microbiology Laboratory is currently performing an in-house study to verify the use of vaginal specimens in this test. In addition, MLabs Clinical Microbiology Laboratory has performed evaluations of specimens that test near the cutoff of the assay and have found that the hc2 assay lacks reproducibility for these specimens. As a result, we have established an equivocal zone and determined that repeat testing of specimens with values in the equivocal zone does not provide a definitive result. We recommend recollecting a specimen for testing if it is clinically warranted (MLabs Test Update 226).

**ACKNOWLEDGEMENTS**

The information contained in this article is adapted from the following:


**REFERENCES**


MLabs Welcomes New Faculty

The University of Michigan Department of Pathology and MLabs Program are pleased to announce that:

Megan Lim, M.D., Ph.D.
will serve as Associate Professor and Director of Hematopathology. Dr. Lim was an Associate Professor of Pathology at the University of Utah where she ran an active research program in the pathobiology of lymphoma, particularly NPM-ALK associated lymphoma. Dr. Lim will continue her active research program and in addition will oversee hematologic tissue banking within the department. Dr. Lim has received numerous awards including the NIH Fogarty Visiting Fellowship, the Canadian Association of Pathology Junior Scientist Award in 2000, the Children’s Oncology Group Young Investigator Award in 2002 and the Translational Research Award in 2004.

Douglas M. Smith, M.D., Ph.D.
joined the faculty as Professor and Director of the HLA Tissue Typing Laboratory in the Division of Clinical Pathology in August 2006. Dr. Smith received his M.D. from the University of Iowa and his Ph.D. in Experimental Pathology from the University of Minnesota while training as a Resident Physician in General Surgery and Otolaryngology. He completed a residency in anatomic and clinical pathology at St. Paul Ramsey Medical Center and his investigations into marrow stem cells and the immune response led him to become Director of Transplant Immunology, first at the University of Nebraska Medical Center and then at the University of Oklahoma Health Sciences Center where he also served as associate director of clinical laboratories. Dr. Smith is subspecialty certified in Blood Banking and Transfusion Medicine and comes to the University of Michigan from his position as the Director of the Transplantation Immunology Laboratory at Baylor University Medical Center.

Test Updates

New Tests

**OXYCODONE, URINE**

Effective September 6, 2006, the toxicology section of the MLabs Chemical Pathology Laboratory will offer testing for oxycodone (Percodan, Percocet, Roxicodone, Oxycontin) and its metabolites in urine. It is a rapid qualitative, competitive binding immunoassay test. The minimum cutoff sensitivity level is 100 ng/mL opiates. The Oxycodone test should be used separately from the standard opiate test when oxycodone use is suspected. The sensitivity detection level of this test is considerably higher than the standard opiate test, which would not detect oxycodone.

**Collection Instructions:** Collect random urine specimen. Refrigerate 5 mL (minimum 1 mL) urine.

**Reference Range:** Negative

Positive results by immunoassay should be considered presumptive. Positive immunoassay results will be confirmed by GC/MS if requested by the client (minimum 10 mL urine required). Qualitative Confirmation is performed by MLabs Drug Analysis and Toxicology Laboratory; quantitative or Forensic/Chain of Custody Confirmation is sent to Warde Medical Laboratory.

**Test Methodology, Reference Range, and Specimen Handling Changes**

**BIOTINIDASE**

Effective July 11, 2006, the Biotinidase assay underwent a specimen type change from serum to EDTA whole blood. There was no change to the reference range.

**Collection Instructions:** Collect specimen in a lavender top tube. Send 3 mL EDTA whole blood refrigerated.

**CALCIUM CHANNEL ANTIBODY TESTS**

Effective June 21, 2006, there was a change to the reference range for the N-Type Calcium Channel Antibody and P/Q-Type Calcium Channel Antibody tests, which are part of the Myasthenia Gravis
(MG)/Lambert-Eaton Syndrome (LES) Evaluation and Paraneoplastic Autoantibody Evaluation panels:

**Reference Range:** N-Type Calcium Channel Ab: <0.02 nmol/L; P/Q-Type Calcium Channel Ab: <0.02 nmol/L

Effective October 19, 2006, there was an additional change to the reference range for the N-Type Calcium Channel Antibody test:

**Reference Range:** N-Type Calcium Channel Ab: < or = 0.03 nmol/L

**CHEMISTRY LABORATORY INSTRUMENTATION CHANGE**

Effective July 18, 2006, the following testing was moved from the Ortho Vitros instruments to the Bayer Advia 2400:

- Alanine Amino Transferase (ALT)
- Albumin
- Alkaline Phosphatase
- Amylase
- Aspartate Amino Transferase (AST)
- Bilirubin
- Calcium
- Carbon Dioxide (CO2)
- Chloride
- Creatinine
- G-Glutamyl Transpeptidase (GGTP)
- Glucose
- Lactic Acid Dehydrogenase (LDH)
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Protein, Total
- Sodium
- Urea Nitrogen
- Uric Acid

In addition, the following changes were made with regard to Bilirubin testing:

- Unconjugated bilirubin, conjugated bilirubin, and delta bilirubin results are no longer reported. Instead, testing includes direct bilirubin, indirect bilirubin, and total bilirubin.
- Bilirubin, Fractionated includes direct bilirubin, indirect bilirubin, and total bilirubin.
- Bilirubin, Total may be ordered alone.
- The Hepatic Function Panel includes total bilirubin and direct bilirubin.
- The Comprehensive Metabolic Panel includes total bilirubin.

These changes were made for all specimen types. Specimen collection and handling requirements did not change. Reference ranges did not change, except as noted below; critical values did not change.

**ALANINE AMINO TRANSFERASE**

**Reference Range:** 7 – 35 IU/L

**ALKALINE PHOSPHATASE**

**Reference Range:** 0-1 year: 50 – 350 IU/L, 1-10 years: 70 – 350 IU/L, 10-16 years: 90 – 420 IU/L, 17-127 years: 30 – 130 IU/L.

**ASPARTATE AMINO TRANSFERASE**

**Reference Range:** 0-1 year: 2 – 70 IU/L, 1-12 years: 5 – 60 IU/L, 12-127 years: 8 – 30 IU/L.

**BILIRUBIN, DIRECT**

**Reference Range:** 1-127 years: < 0.3 mg/dL

**BILIRUBIN, TOTAL**

**Reference Range:** 1 month-12 years: 0.1 – 1.0 mg/dL; 12-127 years: 0.2 – 1.2 mg/dL.

**CARBON DIOXIDE, TOTAL**

**Reference Range:** 1-5 years: 18 – 28 meq/L, 5-12 years: 20 – 28 meq/L, 12-127 years: 20 – 30 meq/L.

**CHLORIDE, SERUM**

**Reference Range:** 0-1 year: 100 – 113 meq/L; 1-127 years: 98 – 108 meq/L.

**CREATININE, SERUM**

**Reference Range:** 1-5 years: 0.2 – 0.6 mg/dL, 5-12 years: 0.4 – 0.9 mg/dL, 12-127 years, male: 0.7 – 1.3 mg/dL, female: 0.5 – 1.0 mg/dL. Estimated Glomerular Filtration Rates (eGFR) for both an African American and a non-African American individual calculated using the MDRD study equation will be reported with serum creatinine levels ordered alone or as part of a panel for patients aged 20 years or older (eGFR will be reported only once every 7 days for inpatients). A GFR estimate between 15 and 59 mL/min for >= 3 months is classified as chronic kidney disease (Stage 3 or 4).

**LACTIC ACID DEHYDROGENASE, SERUM**

**Reference Range:** 1-5 years: 150 – 300 IU/L, 5-12 years: 140– 280 IU/L, 12-127 years: 90 – 190 IU/L.
LIPASE, SERUM
Reference Range: 5 – 50 IU/L.

MAGNESIUM, SERUM
Reference Range: 1.5 – 2.4 mg/dL.

PHOSPHORUS
Reference Range: 0-1 year: 4.8 – 7.0 mg/dL, 1-5 years: 3.8 – 5.8 mg/dL, 5-12 years: 3.5 – 5.6 mg/dL, 12-127 years: 2.7 – 4.6 mg/dL.

CHEMISTRY REFERENCE RANGE CHANGES
The chemistry laboratory conducted a normal range study and a review of reference ranges. Effective October 24, 2006, the following three tests have reference range changes for patients aged 12 - 150 years:

- Calcium, Serum: 8.6 – 10.3 mg/dL
- Carbon Dioxide, Total: 22 – 34 mmol/L
- Lactic Acid Dehydrogenase, Serum: 120 – 240 U/L

CHROMOGRANIN-A
Please note that there has been a change to the specimen collection and handling requirements for the Chromogranin-A assay; this test is now a “strict frozen”. Also note that there has been a change in the reference range effective September 27, 2006.

Collection Instructions: Collect specimen in a red top tube. Centrifuge, aliquot 1 mL (minimum 0.5 mL) of serum into a plastic vial and freeze.

Reference Range: < 160 ng/mL.

CREATINE, URINE
Effective July 6, 2006, Mayo Medical Laboratories replaced their Creatine, Urine assay with a Creatine Disorders Panel, Urine assay. The panel includes creatine, creatinine, guanidinoacetic acid (GAA), and creatine/creatinine ratio and is performed by Liquid Chromatography – Tandem Mass Spectrometry (LC-MS/MS) Stable Isotope Dilution Analysis.

This test is useful for the evaluation of patients with a clinical suspicion of inborn errors of creatine metabolism, including arginine: glycine amidinotransferase (AGAT) deficiency, guanidinoacetate methyltransferase (GAMT) deficiency and cellular transport (CrT1) defects.

Collection Instructions: Send 1 mL aliquot from random urine collection. Freeze.

Reference Range: Interpretive report provided.

CYANIDE, BLOOD
Effective August 7, 2006, Cyanide, Blood, testing is sent to Mayo Medical Laboratories.

Collection Instructions: Collect specimen in a lavender top tube. Send 3 mL of whole blood at room temperature.

Reference Range: < 0.2 μg/mL.

DIGOXIN
For many years the accepted therapeutic ranges for serum Digoxin have been 0.5 – 1.5 ng/mL or 0.5 – 2.0 ng/mL. These ranges were designed to reduce toxicity, but were not necessarily reflective of drug efficacy and long-term benefit.

Two recent post-hoc analyses of data from a randomized clinical trial of patients with chronic heart failure have demonstrated that serum digoxin concentrations within the generally accepted reference range may increase the risk of death (1,2). Specifically, the results show the following associations:

- Digoxin concentrations of 0.5 to 0.8 ng/mL have a lower rate of all-cause mortality in chronic heart failure patients.
- Digoxin concentrations of 0.9 to 1.1 ng/mL have a risk for all-cause mortality similar to placebo controls.
- Digoxin concentrations of 1.2 ng/mL and above are associated with an increased risk of all-cause mortality in chronic heart failure patients.

Although the mechanism by which digoxin concentrations of 1.2 – 2.0 ng/mL increase the risk for all-cause mortality is unclear, the results of these reports provide evidence that the upper limit of the current therapeutic ranges should be adjusted downward.

Based on the studies, plus consultation with the Cardiology and Pharmacy departments at the University of Michigan, beginning August 30, 2006, the Chemical Pathology Laboratory will no longer report a general reference range of 0.5 – 1.5 ng/mL, but will instead provide an interpretive comment for each serum digoxin result that states the following:

In a retrospective analysis of data from a randomized clinical trial of patients with chronic heart failure, the following associations were observed between serum digoxin concentrations and all-cause mortality:

- 0.5 to 0.8 ng/mL, lower risk than placebo
- 0.9 to 1.1 ng/mL, similar risk to placebo
- 1.2 ng/mL and above, higher risk than placebo

Digoxin results above 1.1 ng/mL will flag as “H” (high) and the critical value limit will change from 2.5 ng/mL to 2.0 ng/mL.
REFERENCES:


DRUG SCREEN, MECONIUM

Meconium specimens are occasionally cancelled because the specimen is QNS for screening and confirmation. Please note that the specimen collection instructions have been modified to reflect the fact that multiple meconium specimens can be combined in order to achieve sufficient quantity for testing.

Collection Instructions: Place diaper liner (plastic wrap) into diaper. Transfer entire meconium specimen to plastic screw-capped container. Insert new diaper liner and continue collecting into the same container until 2 - 5 grams of meconium are collected or until the first milk stool appears. Refrigerate specimen between collections.

ELECTROLYTE REPORTING

Beginning Monday, September 18, 2006, electrolyte results will be reported in units of mMol/L instead of meq/L. This will standardize reporting between instruments and reports, as well as with ionized calcium. This change affects the following tests:

- Carbon Dioxide, Total
- Chloride, Serum
- Chloride, Urine, Random
- Chloride, Fluid
- Potassium, Serum
- Potassium, Urine, Random
- Potassium, Fluid
- Sodium, Serum
- Sodium, Urine, Random
- Sodium, Fluid
- Electrolyte Panel
- Basic Metabolic Panel
- Comprehensive Metabolic Panel
- Renal Function Panel

HISTOPLASMA ANTIBODY

Mayo Medical Laboratories has made a change to their Histoplasma Antibody assay. Effective July 11, 2006, this test is performed by Enzyme Immunoassay (EIA). If the EIA screen is positive or equivocal, Histoplasma Antibody by Complement Fixation/Immunodiffusion will be performed at an additional charge.

HYPERSENSITIVITY PNEUMONITIS IGG ANTIBODIES

New age-specific reference values for Micropolyspora faeni, Thermactinomyces vulgaris, and Aspergillus fumigatus IgG Antibodies were implemented effective July 12, 2006:

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;13 yrs</th>
<th>13–18 yrs</th>
<th>&gt;18 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. fumigatus</td>
<td>≤ 20.6 mg/L</td>
<td>≤ 67.2 mg/L</td>
<td>≤ 80.1 mg/L</td>
</tr>
<tr>
<td>M. faeni</td>
<td>≤ 4.9 mg/L</td>
<td>≤ 9.1 mg/L</td>
<td>≤ 13.2 mg/L</td>
</tr>
<tr>
<td>T. vulgaris</td>
<td>≤ 6.6 mg/L</td>
<td>≤ 11.0 mg/L</td>
<td>≤ 23.9 mg/L</td>
</tr>
</tbody>
</table>

INSULIN-LIKE GROWTH FACTOR (IGF-1)

Beginning September 13, 2006, Insulin-Like Growth Factor has changed from an RIA to a chemilumininescent enzyme immunoassay methodology. Specimen collection and handling requirements have not changed. The reference ranges have changed. The following are the new ranges for both males and females:

Reference Range: 1-2 yrs 51 - 315 ng/mL; 3-5 yrs 49 - 286 ng/mL; 6-7 yrs 50 - 315 ng/mL; 8 yrs 64 - 345 ng/mL; 9 yrs: 74 - 388 ng/mL; 10 yrs 88 - 452 ng/mL; 11 yrs 111 - 551 ng/mL; 12 yrs: 143 - 693 ng/mL; 13 yrs: 183 - 850 ng/mL; 14 yrs: 220 - 972 ng/mL; 15 yrs: 237 - 996 ng/mL; 16 yrs 226 - 903 ng/mL; 17 yrs: 193 - 731 ng/mL; 18 yrs: 163 - 584 ng/mL; 19 yrs: 141 - 483 ng/mL; 20 yrs: 127 - 424 ng/mL; 21-25 yrs 116 - 358 ng/mL; 26-30 yrs: 117 - 329 ng/mL; 31-35 yrs: 115 - 307 ng/mL; 36-40 yrs: 109 - 284 ng/mL; 41-45 yrs: 101 - 267 ng/mL; 46-50 yrs: 94 - 252 ng/mL; 51-55 yrs: 87 - 238 ng/mL; 56-60 yrs: 81 - 225 ng/mL; 61-65 yrs: 75 - 212 ng/mL; 66-70 yrs: 69 - 200 ng/mL; 71-75 yrs: 64 - 188 ng/mL; 76 yrs: 57 - 171 ng/mL.

LYMPHOCYTE ANTIGEN PROLIFERATION ANALYSIS

Effective September 27, 2006, there has been a change in the specimen volume requirement for Lymphocyte Antigen Proliferation Analysis to 20 mL (minimum 15 mL) of ACD whole blood.

NTX-TELOPEPTIDE, URINE

Effective September 6, 2006, Mayo Medical Laboratories made a reference range change to the NTx-Telopeptide, Urine, assay to reflect the addition of pediatric ranges:

MLabs News

800 NUMBER

Please note: MLabs nationwide toll-free Client Service number is 800-862-7284. (The additional number 800-537-7284 for calling from outside Michigan has been eliminated.)

NEW AND IMPROVED MLABS WEB PAGE

MLabs is pleased to announce that we have redesigned and updated our web page to make it easier for you to find the information you need. Please visit our site at www.mlabs.umich.edu.

U-M DEPARTMENT OF PATHOLOGY NEWS

Henry D. Appelman, M.D., has been appointed as President of the OESO, the Organization for the Statistical Study of Diseases of the Esophagus, an international association of the most renowned and accomplished esophagogologists in the world that is headquartered in Paris. This society includes gastroenterologists, esophageal surgeons, physiologists, biochemists, radiologists and pathologists.

Barbara J. McKenna, M.D., Associate Professor has been elected Vice-President of the American Society for Clinical Pathology (ASCP). Founded in 1922, the American Society for Clinical Pathology is a professional society with 140,000 member pathologists and laboratory professionals and provides excellence in education, certification, and advocacy on behalf of patients, pathologists, and laboratory professionals. Dr. McKenna is also the Commissioner for the ASCP’s Commission on Medical Education in Pathology and the Director of the annual Resident Review Course.

GENETIC TESTING FOR M-CARE MEMBERS

M-CARE recently announced the need to obtain prior authorization for genetic assessment and testing for M-CARE HMO/POS members (excluding M-CARE Secure). M-CARE communicated that any genetic testing related to pregnancy whether preconceptual or prenatal, regardless of ordering physician does not need prior authorization.

Please note that non-obstetrically related genetic testing requires authorization. The following steps must be completed to ensure proper reimbursement:

- The provider who requests testing must obtain prior authorization from M-CARE. Clinical information is required to demonstrate medical necessity.
- The provider who performs testing should verify, prior to rendering genetic assessment or testing, that authorization has been obtained.

Authorizations can be obtained and verified through the M-CARE Authorization Department by calling 800-527-5549, extension 2271, or by logging on to M-CARE Connect (if provider is registered).

SALE OF M-CARE TO BLUE CROSS

On Friday, September 22, the University of Michigan Board of Regents approved the sale of the University’s M-CARE health plan to Blue Cross Blue Shield of Michigan and its subsidiary, Blue Care Network of Michigan. The sale will also require approval from government regulators, a process that could take several months or even longer. It is anticipated that the government approval process could be completed by late 2006 or early 2007.

M-CARE products will remain in place after the sale and through the duration of the contract the employer group has with M-CARE. This means M-CARE members will continue to have their M-CARE products will remain in place after the sale and through the duration of the contract the employer group has with M-CARE. This means M-CARE members will continue to have their

Further information and updates on the proposed sale, and background information on M-CARE, is available online at www.med.umich.edu/mcareupdate. That site also includes information for M-CARE employees, members, providers and other audiences.