Muir-Torre Syndrome and Mutations in Mismatch Repair Proteins

Douglas R. Fullen, M.D., Associate Professor of Pathology and Dermatology

Sebaceous neoplasms are uncommon tumors in the skin. These tumors may be benign, as in sebaceous adenomas or sebaceous epitheliomas (sebaceomas), or malignant, as in sebaceous carcinomas. The significance of sebaceous neoplasms, beyond predicting the biologic behavior and optimal treatment of an individual tumor, lies in the association of a subset of these tumors with the Muir-Torre syndrome (MTS).

Muir in 1967 and Torre in 1968 independently described patients with sebaceous tumors of the skin and intestinal malignancies. This autosomal dominant inherited genodermatosis, which has a high degree of penetrance yet variable expression, subsequently became known as the MTS. Sebaceous neoplasms, keratoacanthomas, and visceral malignancies characterize this syndrome. The most common visceral malignancies are colorectal and genitourinary carcinomas, accounting for approximately 50% and 25% of cases, respectively. Other tumors, such as carcinomas of the breast, upper aerodigestive tract, lung, endometrium, and ovaries, also may occur in the MTS but at a much lower frequency. Importantly, multiple visceral malignancies occur in nearly half of all patients with this syndrome, necessitating close clinical follow-up and frequent screening. Interestingly, however, the visceral malignancies in MTS usually behave in a less aggressive manner when compared to similar tumors arising sporadically in patients. The identification of a patient with the MTS should also prompt screening of other family members at risk of inheriting the specific mutation responsible for this syndrome.

While any type of sebaceous neoplasm may occur in MTS, sebaceous adenoma is the most common form, with the cystic variant appearing to be the most specific subset. Furthermore, sebaceous tumors arising in patients less than 50 years of age or arising at anatomic sites other than the face and scalp are more likely to be associated with the MTS.

Early speculation held that MTS was a variant of hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome because of the presence of rare cutaneous neoplasms in patients with HNPCC.
This close association has subsequently been proven by detection of mutations in the same mismatch repair (MMR) proteins in patients with MTS and patients with HNPCC. These MMR proteins are essential for maintaining the integrity of deoxyribonucleic acid (DNA) by removing mismatches of nucleotide bases that arise from small insertions or deletions in genes during faulty DNA replication. A germline mutation in one of the MMR proteins leads to the lack of repair and subsequent accumulation of replication errors culminating in genetic instability. This genetic instability also involves microsatellites, which are short segment nucleotide repeats, and can be demonstrated as microsatellite instability (MSI) in tumors by molecular testing with a panel of probes which target five specific loci. Thus, the presence of MSI correlates strongly with germline mutations in one or more MMR proteins.

Multiple MMR proteins have been elucidated and include, but are not limited to, MLH1, PMS2, MSH2, and MSH6. In HNPCC patients, germline mutations occur with similar frequency in MSH2 and MLH1. In contrast, the majority of germline mutations in MTS patients occur in MSH2 followed in frequency by MLH1 and MSH6. Interestingly, MSH2 and MSH6 and MLH1 and PMS2 form heterodimers, so that when there is loss of one gene product there is loss of the corresponding gene product of the pair.

Recently, monoclonal antibodies with specificity for the commonly mutated MMR proteins have been developed for immunohistochemistry. These antibodies against MLH1, PMS2, MSH2, and MSH6 can be applied to paraffin-embedded sections of tumor samples to determine whether tumor nuclei have normal expression or have lost expression as a manifestation of a mutation. The results of these immunostains generally correlate well with MSI testing and can serve to screen patients for MTS. The availability of these stains raises an important question. Should all patients with a sebaceous neoplasm be screened by immunohistochemical staining against the MMR proteins? Given the relative rarity of sebaceous neoplasms, some authors have advocated testing all sebaceous tumors for loss of MMR proteins. However, the decision to perform a test that potentially defines a cancer susceptibility gene mutation is probably best made by consultation between the patient and patient’s physician.

In summary, MTS is a variant of Lynch syndrome and is characterized by sebaceous neoplasms and keratoacanthomas of the skin in conjunction with at least one visceral malignancy, most often a colorectal carcinoma. Sebaceous neoplasms take the form of adenomas, sebaceomas, and carcinomas, with adenomas being the most common tumor in the MTS. Testing for MTS includes immunohistochemistry with antibodies against specific MMR proteins, namely MLH1, PMS2, MSH2, and MSH6, microsatellite instability testing, and mutational analysis of specific genes. Immunohistochemical stains are extremely useful in screening for MMR mutations because of their high sensitivity and specificity. These antibodies have recently been evaluated in the Immunohistochemistry Laboratory at the University of Michigan and are now available for testing in patients with sebaceous neoplasms in whom MTS is a clinical consideration.
REFERENCES


Spotlight on Douglas Fullen, M.D.

Associate Professor of Pathology and Dermatology

Board Certified in Anatomic and Clinical Pathology and Dermatopathology

Dr. Fullen received his M.D. degree from Emory University. Dr. Fullen completed his residency training in Anatomic and Clinical Pathology at the University of Michigan and his fellowship in Dermatopathology at The New York Presbyterian Hospital - Cornell University Weill Medical College in New York. He was a Clinical Assistant Professor in the Department of Pathology at the Albany Medical College prior to joining the faculty of the Department of Pathology at the University of Michigan in 2000. A talented, respected teacher, Dr. Fullen has been recognized for his outstanding contribution to the education of medical students, residents in both Pathology and Dermatology, and dermatopathology fellows. He currently serves as the Director of the Dermatopathology Fellowship and Co-director of the Dermatopathology Section in the Department of Pathology at the University of Michigan. His clinical interest is in all areas of Dermatopathology, with special interest in melanocytic tumors, non-melanoma skin cancers, and diagnosis of immunobullous disorders of the skin and mucosae via direct immunofluorescence.

Dr. Fullen’s research involves collaboration with many investigators in the Departments of Pathology, Dermatology, Surgery, Otolaryngology, Obstetrics and Gynecology, and Internal Medicine at the University of Michigan, and in the Life Sciences Institute at the University of Michigan. He has authored or co-authored over 45 peer-reviewed articles and multiple book chapters, and serves as a reviewer of articles for many leading journals in his field and of abstracts submitted for the Dermatopathology Section at the annual meeting of the United States and Canadian Academy of Pathology. He is a member of the American Society of Dermatopathology, American Academy of Dermatology, United States and Canadian Academy of Pathology, and Society for Melanoma Research. His current research interest is focused primarily on the application of molecular techniques to melanocytic tumors and Merkel cell carcinoma to understand the biologic behavior and most appropriate treatment of these tumors.

MLabs Spectrum 3
Continuing Medical Education Opportunity

ADVANCES IN FORENSIC MEDICINE AND PATHOLOGY

May 5 – 6, 2010
The Inn at St. Johns, Plymouth, Michigan
University of Michigan Department of Pathology

This two day conference presents a timely examination of current controversies and advances in the field of forensic medicine and pathology. The Keynote Speaker, Dr. Andrew Baker, the chief medical examiner in Minneapolis will discuss infant death investigation including radiological and histological correlation of fractures. Dr. Baker also will discuss the management of the Minneapolis Bridge Collapse disaster and implications for disaster preparedness. In addition, speakers will discuss advances in molecular applications to sudden cardiac death, pharmacogenomics, and the new science of computer-assisted injury identification. Other topics include doll reenactment training, new requirements for Canadian death investigation, and clinical forensic medicine.

This conference content is intended for pathologists, physicians, death investigators, law enforcement personnel, attorneys, and child protection practitioners.

The program has been approved for 13.5 AMA CME credits. Contact the University of Michigan Medical School Office of CME Monday through Friday between 8 a.m. and 5 p.m. for more information or to register:

Phone: 734-763-1400 or 800-800-0666
Fax: 734-936-1641
E-mail: OCME@umich.edu

Test Updates

New Tests

CYSTATIN C

Effective December 1, 2009, Cystatin C testing is performed by the MLabs Chemical Pathology Laboratory.

Cystatin C is produced by all nucleated cells at a constant rate and the production rate in humans appears to be constant over the entire lifetime. Elimination from the circulation is almost entirely via glomerular filtration. The serum concentration of Cystatin C is independent of muscle and gender in the age range of 1 to 50 years. It has been proposed that Cystatin C in serum or plasma is a more sensitive marker for GFR and superior to serum creatinine for estimation of GFR. Cystatin C may also be of value as a prognostic marker for acute heart failure.

Collection Instructions: Collect specimen in a red top or SST tube. Centrifuge, aliquot 0.5 mL (minimum 0.25 mL) of serum into a plastic vial and refrigerate.

Reference Range: 1-17 years: 0.50 - 1.25 mg/L; 18-150 years: 0.50 - 1.00 mg/L.

MMGL HEARING LOSS ASSAYS

The Molecular Genetics Laboratory of The Michigan Medical Genetics Laboratories (MMGL) recently brought two new assays in-house:

Connexin 30 (GJB6) Mutation Analysis

The MMGL Molecular Genetics Laboratory brought Connexin 30 (GJB6) Deletion Analysis testing in-house effective January 4, 2010. Connexin 30 testing can be ordered individually or as a reflexive test for patients who have had Connexin 26 testing with no or only one pathogenic mutation detected in GJB2. This test is used for confirmation of a diagnosis of hearing loss with a genetic etiology and for carrier testing in families with a known GJB2 mutation.

Connexin testing will be performed as a sequential reflexive assay consisting of Connexin 26 (GJB2) Mutation Analysis and Connexin 30 (GJB6) Deletion Analysis. A patient with non-syndromic hearing loss can have two mutations in Connexin 26, two mutations in Connexin 30, or one mutation in Connexin 26 and one mutation in Connexin 30. Mutations in the GJB2 (Connexin 26) gene account for 30-70% of non-syndromic recessive
(and a small number of autosomal dominant) deafness in Caucasian populations. Approximately 40% of individuals with sporadic non-syndromic hearing loss also carry GJB2 mutations.

Testing will begin with Connexin 26 (GJB2) mutation analysis, and will be followed by Connexin 30 (GJB6) deletion analysis at an additional charge if zero or one pathogenic mutation is found in the GJB2 gene. By ordering this test the clinician acknowledges that additional reflex testing will be performed and billed at a separate additional charge if indicated. Connexin 30 (GJB6) deletion analysis may also be ordered individually (order code CX30DS). By ordering this test the clinician acknowledges that informed consent has been obtained from the patient as required by applicable state or federal laws and the ordering clinician has authorization from the patient permitting MLabs to report the test results to the ordering clinician.

Collection Instructions: Collect specimen in a lavender top tube. Send intact specimen within 24 hours if stored at room temperature or within 5 days if stored refrigerated. Obtaining informed consent from the patient prior to genetic testing is strongly recommended. If desired, a UMHS Request and Consent for Genetic Testing form can be obtained from the MMGL Molecular Genetics Laboratory by contacting the MLabs Client Services Center at 800-862-7284.

SLC17A8 Mutation Detection

The MMGL Molecular Genetics Laboratory began SLC17A8 632C>T (A211V) mutation detection testing in-house on Monday, February 1, 2010. SLC17A8 testing will detect for the presence of the 632C>T (A211V) mutation in patients with nonsyndromic deafness.

Collection Instructions: Collect specimen in a lavender top tube. Send intact specimen within 24 hours if stored at room temperature or within 5 days if stored refrigerated. Include the patient’s family history, pedigree, and ethnicity on the test requisition. Obtaining informed consent from the patient prior to genetic testing is strongly recommended. If desired, a UMHS Request and Consent for Genetic Testing form can be obtained from the MMGL Molecular Genetics Laboratory by contacting the MLabs Client Services Center at 800-862-7284.

THROMBOTIC RISK PROFILE

Effective January 25, 2010, the MLabs Coagulation Laboratory began offering a Thrombotic Risk Profile for use as a comprehensive study to determine the causes of venous thrombosis. This test will replace the Prothrombic Evaluation panels.

The Thrombotic Risk Profile will include a PT (Prothrombin Time), PTT (Activated Partial Thromboplastin Time), Antithrombin III Activity, Factor VIII Assay, Fibrinogen (clottable), Fibrinogen Antigen, Plasminogen Activity, Protein C Activity, Protein S Antigen (Free), Activated Protein C Resistance, Hexagonal Phospholipid Neutralization, and Dilute Russell’s Viper Venom Test.

The following tests are not included in the profile, but may also be considered as part of an evaluation for a prothrombic state: Cardiolipin Antibody, Plasma Homocysteine, and Prothrombin 20210 Mutation Detection.

Collection Instructions: Collect specimens in blue top (citrate 3.2%) tubes. Mix by inversion. Specimens should arrive at lab within 2 hours of collection; transport at room temperature. Alternatively, centrifuge, aliquot plasma into seven (7) polypropylene plastic vials (1 mL each), and freeze the specimens within 2 hours of collection. Transport frozen specimens on dry ice. If specimen is drawn through an indwelling catheter, the line should be flushed with 5 mL of saline and the first 5 mL of blood or six times the deadspace volume of the catheter being used discarded. Specimens will be rejected if not properly filled, clotted, grossly hemolyzed, or contaminated with heparin.

Test Methodology, Reference Range, and Specimen Handling Changes

17-HYDROXYPREGNENOLONE & PREGNENOLONE


17-Hydroxypregnenolone and Pregnenolone are used as ancillary tests for congenital adrenal hyperplasia (CAH), particularly in situations in which a diagnosis of 21-hydroxylase and 11-hydroxylase deficiency have been ruled out and for confirming diagnoses of 3b-hydroxysteroid dehydrogenase (3b-HSD) deficiency and 17-alphahydroxylase deficiency. 17-Hydroxypregnenolone is
also used as part of a battery of tests to evaluate females with hirsutism or infertility, both of which can result from adult-onset CAH.

Collection Instructions: Collect specimen in a red top tube. Centrifuge, aliquot 0.5 mL into a plastic vial and freeze.

**17-HYDROXYSTEROIDS & 17-KETOSTEROIDS, URINE**

Due to low test volumes, the MLabs Special Chemistry Laboratory discontinued performing 17-Hydroxysteroids and 17-Ketosteroids, Urine, effective September 1, 2009. Requests for these tests will be sent to Esoterix Laboratory Services (tests #500230 17-Ketosteroids, Urine and #500216 17-Hydroxycorticosteroids, Urine, respectively).

Collection Instructions: Collect 24 hour urine specimen. Add boric acid (0.5 gm/100 mL) as a preservative. Mix well, measure 24 hour urine volume, aliquot 50 mL (minimum 5 mL) into a plastic urine container and freeze. Record total 24 hour urine volume and collection dates/times on request form.

**BETA 2 GLYCOPROTEIN 1 ANTIBODY PANEL**

Beginning January 20, 2010, Beta-2 Glycoprotein 1 Antibody Panel is performed using a new manufacturer (INOVA) assay kit. Due to the acquisition of The Binding Site Group by INOVA Diagnostics, the Binding Site kit is being discontinued. There will be no change to specimen collection and handling.

Reference Range: B2GP1 IgG: Negative (<20 SGU); B2GP1 IgM: Negative (<20 SMU); B2GP1 IgA: Negative (<20 SAU).

**BILE ACIDS, TOTAL**


Collection Instructions: Collect specimen in a red top tube from a fasting patient. Centrifuge, aliquot 1 mL of serum into a plastic vial and refrigerate.

Reference Range: < or = 10 µmol/L

**BLASTOMYCYES ANTIBODY**

Due to reagent unavailability, the complement fixation part of Mayo Medical Laboratories Blastomyces Antibody tests will no longer be performed effective January 5, 2010. The immunodiffusion component will remain unchanged. Note that these changes will also apply to the Blastomyces components of the Fungal Antibody Panels.

Collection Instructions: Collect specimen in a red top or SST tube. Centrifuge, aliquot 0.5 mL of serum into a plastic vial and refrigerate. CSF is also acceptable.

**C5 COMPLEMENT ANTIGEN**

Effective November 3, 2009, there was a change to the reference range for Mayo Medical Laboratories C5 Complement Antigen assay:

Reference Range: 10.6 - 26.3 mg/dL

**CYCLIC CITRULLINATED PEPTIDE (CCP) ANTIBODY**

Beginning January 19, 2010, Cyclic Citrullinated Peptide (CCP) Antibody is performed using a new manufacturer (INOVA) assay kit. Due to the acquisition of The Binding Site Group by INOVA Diagnostics, the Binding Site kit is being discontinued. There will be no change to specimen collection and handling. Note that the INOVA CCP test kit detects IgG and IgA antibodies; it does not detect IgM antibodies.

Reference Range: 0 – 19 Units

**DIURETICS SCREEN, URINE**

Mayo Medical Laboratories has discontinued their Diuretics Screen, Qualitative, Urine, effective November 18, 2009. Requests for this test will be sent to MedTox Laboratories.

Collection Instructions: Collect random urine and refrigerate.

Reference Range: Negative. Qualitative diuretic screen includes: benzthiazide, bumetanide, chlorothiazide, chlorthalidone, furosemide, hydrochlorothiazide, hydroflumethiazide, and metolazone.

**DRUG MONITORING TEST CHANGES**

Mayo Medical Laboratories has recently made changes to the specimen requirements, reference ranges, and reporting units for a number of drug monitoring tests; note that plasma specimens are no longer acceptable for these assays:

- **5-Flucytosine**, effective 2/11/10
  Reference Range: Peak: >25 mcg/mL, Toxic: >100 mcg/mL.

- **Disopyramide**, effective 12/29/09
  Reference Range: Therapeutic: 2.0 - 5.0 mcg/mL; Toxic: >7.0 mcg/mL.
**Gabapentin**, effective 12/29/09
Reference Range: 2.0 - 20.0 mcg/mL.

**Itraconazole**, effective 12/29/09
Reference Range: Itraconazole (trough): >0.5 mcg/mL (localized infection); >1.0 mcg/mL (systemic infection). Hydroxyitraconazole: No therapeutic range established; activity and serum concentration are similar to parent drug.

**Mexiletine**, effective 10/27/09
Reference Range: Therapeutic: 0.8 - 2.0 mcg/mL; Toxic: greater than 2 mcg/mL.

**Propafenone (Rhythm),** effective 10/27/09
Reference Range: 0.5 - 2.0 mcg/mL.

**Trimethoprim**, effective 2/11/10
Reference Range: >2.0 mcg/mL.

**Warfarin**, effective 10/27/09
Reference Range: Therapeutic: 2.0 - 5.0 mcg/mL; Toxic: > or = 10.0 mcg/mL.

**FLECAINIDE**
Effective October 19, 2009, requests for Flecainide are sent to Warde Medical Laboratories.

Collection Instructions: Collect specimen in a red top tube; do not use SST tube. Centrifuge, aliquot 1 mL (minimum 0.2 mL) of serum into a plastic vial and refrigerate.

Reference Range: Therapeutic: 0.2 - 1.0 µg/mL; Toxic >1.0 µg/mL.

**HEPATITIS B VIRUS DNA BY PCR, QUANTITATIVE**

The reference range for the MLabs Microbiology Laboratory’s Hepatitis B Virus DNA by PCR assay has changed effective November 25, 2009. The upper linear limit has not changed (110,000,000 IU HBV DNA, Log10 = 8.04). Viral levels detected below the lower linear limit will be reported as HBV DNA detected, < 29.0 HBV DNA, Log10 = < 1.46.

Reference Range: < 29.0 HBV DNA IU/mL

**HIV TYPE 1 PROVIRAL DNA BY PCR, QUALITATIVE**

The MLabs Microbiology Laboratory has discontinued the HIV Type 1 Proviral DNA by PCR assay effective August 20, 2009, due to low test volume. This test is used for detection of HIV-1 proviral DNA in patients recently exposed to HIV virus, but prior to production of HIV-specific antibodies. Requests for this test will be sent to Mayo Medical Laboratories.

Collection Instructions: Collect specimen in a lavender top (EDTA) tube. Send 2 mL of whole blood in a screw-capped vial; refrigerate up to 2 days or freeze for longer storage.

Reference Range: Negative.

**INSULIN ANTIBODY**

Effective October 23, 2009, changes were made to the specimen requirements and reference range for Mayo Medical Laboratories Insulin Antibody assay as follows:

Collection Instructions: Collect specimen in a red top or SST tube from a fasting patient. Centrifuge, aliquot 1 mL (minimum 0.5 mL) of serum into plastic vial and refrigerate. Grossly hemolyzed specimens are unacceptable.

Reference Range: < or = 0.02 nmol/L

**POSACONAZOLE**

Effective August 25, 2009, Mayo Medical Laboratories began performing Posaconazole testing in-house.

Collection Instructions: Collect specimen in a red top tube. Centrifuge, aliquot 2 mL (minimum 0.6 mL) of serum into a plastic vial and freeze.

Reference Range: >700 ng/mL

**THYROTROPIN RECEPTOR ANTIBODY**

Effective August 25, 2009, Mayo Medical Laboratories transitioned the Thyrotropin Receptor Antibody assay to an Electrochemiluminescence Immunoassay (ECLIA) test methodology.

Reference Range: < or = 1.75 IU/L

**Discontinued Test**

**SPERM ANTIBODIES, CERVICAL MUCUS**

Mayo Medical Laboratories has discontinued Sperm Antibody testing on cervical mucus specimens effective October 30, 2009. Testing is available on Serum, Semen (direct) and Seminal Plasma (indirect) specimens.
MLabs News

U-M DEPARTMENT OF PATHOLOGY NEWS

MLabs is pleased to announce that Jason Cheng, M.D., Ph.D., will join the hematopathology faculty as an Assistant Professor effective April 1, 2010. Dr. Cheng completed his residency and fellowship in hematopathology at the University of Chicago Medical Center. One of Dr. Cheng’s goals will be to establish a laboratory for epigenetic profiling of tumors, particularly myelodysplastic syndrome and acute myelogenous leukemia.

Arul M. Chinnaiyan, M.D., Ph.D., S.P. Hicks Professor and Professor of Pathology and Urology, was one of three investigators to receive the Paul Marks Prize for Cancer Research by the Memorial Sloan-Kettering Cancer Center.

MLabs is pleased to announce that Priya Kunju, M.D., Assistant Professor of Pathology, assumed Directorship of the Genitourinary Fellowship effective January 1, 2010.

Lindsay Schmidt, M.D., who is currently a Pulmonary Pathology Fellow in the Division of Anatomic Pathology, will be joining the faculty as an Assistant Professor effective July 1, 2010.

Effective January 1, 2010, Dan Visscher, M.D., assumed administrative responsibility for our Breast Fellowship as Program Director. The long standing success of our fellowship is a tradition that began with the late Dr. Hal Oberman and was nurtured by his successor, Dr. Celina Kleer.

TISSUE TYPING FOR DISEASE ASSOCIATION PATIENTS

The MLabs Histocompatibility (Tissue Typing) Laboratory is accredited by the American Society for Histocompatibility and Immunogenetics (ASHI). Due to an ASHI regulation concerning Disease Association patients, MLabs will now require that the specific Disease and HLA Antigen being requested are provided with each request for HLA typing. For example, the request might state: HLA typing for B51 for Behcet’s Disease.

Please refer to the reference below for a partial listing of HLA associated disease risks:

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<thead>
<tr>
<th>Disease or Association</th>
<th>Associated HLA Antigen or Allele</th>
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<tr>
<td>Ankylosing Spondylitis</td>
<td>HLA-B2</td>
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<td>Inflammatory Eye Diseases:</td>
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<td>Uveitis</td>
<td>HLA-B27</td>
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<td>Bird Shot Retinopathy</td>
<td>HLA-A29</td>
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<td>Behcet’s Disease</td>
<td>HLA-B51</td>
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<td>Thygeson’s Keratitis</td>
<td>DR17 (DR3)</td>
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<td>Vogt-Koyanagi-Harada’s Disease</td>
<td>DRB1*0404/05/07 and/or *0410</td>
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<td>MDS Immunotherapy Candidate (e.g., ATG)</td>
<td>DR15</td>
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<tr>
<td>Celiac Disease</td>
<td>DQ2 or DQ8 (DQB1*0201, *0202, or *0302)</td>
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<td>Narcolepsy</td>
<td>DQB1*0602</td>
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<td>Rheumatoid Arthritis</td>
<td>Several DRB1 alleles</td>
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<tr>
<td>Abacavir Hypersensitivity</td>
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<td>Carbamazepine Hypersensitivity</td>
<td>HLA-B*1502</td>
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<td>Melanoma Vaccine Eligibility</td>
<td>HLA-A*0201</td>
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<tr>
<td>Antibiotic Refractory Lyme Arthritis</td>
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