Russell Tracy, Ph.D. and research on risk factors for myocardial infarction and atherosclerosis

**ALSO FEATURED:** GI Pathologists  Microscopy Outreach  Publications & Grants  Clinical News
Letter from the chair

The members of our Department of Pathology and Laboratory Medicine have had a great year. We are moving forward with our Strategic Plan with initiatives across Our People, High Value Patient Care, Living Our Academic Mission, and Supporting the Mission. We are active in clinical care, teaching, research, and local, national and international service. One of the most exciting advances over the past several years has been to coalesce as one Department, which has been evidenced by our Grand Rounds combining research and clinical talks attended by all faculty and trainees, and by the growing number of collaborative research projects between our clinical and research faculty. This inaugural issue of our newsletter, PATHways, highlights many of our accomplishments over the past year, a few longstanding projects, such as Project MICRO and the translational research of our Laboratory for Clinical Biochemistry Research, as well as updates on some of our new projects, such as our Genomic Medicine Program and our Pathology Student Fellowship Endowment. I am very proud of all our accomplishments, and very pleased to share some of these through this Newsletter.

Debra G.B. Leonard, M.D., Ph.D.
Chair and Professor of Pathology & Laboratory Medicine
Bench to Bedside: Translational Research at the LCBR
By Margaret Doyle, Ph.D.

Bench to bedside is the catchphrase frequently used in research to justify the ultimate goal of basic research, which is to improve the health of the people we serve. But in the Department of Pathology and Laboratory Medicine at the University of Vermont, these are more than just words. Translating research findings to clinical practice is central to the goal of the Laboratory of Clinical Biochemistry Research, or LCBR, led by Russell Tracy, Ph.D. Located in UVM research facilities in Colchester, VT, the LCBR group of over 30 people serves as a core laboratory for national clinical population-based studies. The function of the laboratory is not just to perform assays for these studies, but to offer the expertise required to implement these studies from inception through analysis and publication. From this collaborative work over decades, the LCBR is home to a biorepository of more than two million samples from over 60,000 research participants. The LCBR research focuses on chronic diseases including cardiovascular disease, lung diseases, aging, diabetes, HIV, and trauma.

How does research translate from bench to bedside?
One of the main goals of the LCBR is biomarker discovery. Working with large cohort studies, samples (blood, urine, and/or tissues) are collected and stored over time from volunteers, as well as demographic and pertinent medical information (depending on study protocols). These samples are analyzed for potential biomarkers that may be better for prediction, diagnosis or staging of disease compared to standard methods. The options for potential biomarkers are extensive and continuously growing, and many biomarkers are discovered by the basic science research performed in the LCBR. For example, recent work on the role of adaptive immune cells in preclinical atherosclerosis evolved from basic mouse model research performed in the laboratory of Dr. Sally Huber in the LCBR.

One Success Story
One success story for bench to bedside translation is C-reactive protein (CRP). CRP is an acute phase reactant protein, whose levels increase substantially in response to infection or tissue injury. Laboratory tests for CRP have been in clinical use for years, but CRP values for healthy individuals were not available. This lack of normal values was because the early methods for measuring CRP were not sensitive enough to detect the low CRP levels in healthy individuals. The development of a highly sensitive CRP assay by the LCBR in the late 1990s allowed measurement of CRP levels in a healthy population. As part of the assay validation process, biovariability studies included repeated CRP measurements on the same individuals over months which demonstrated that although an individual’s CRP level may vary over time, the average levels between individuals was quite different. This sensitive assay (hs-CRP) was used in population studies to examine its predictive ability alone, or in addition to current risk predictors, in a wide array of clinical and preclinical disease states, such as coronary heart disease, atherosclerosis, stroke, cognitive disorders, and HIV.

Into the Clinic
Today, the hs-CRP is available in most clinical laboratories. According to Greg Sharp, M.D., Director of Chemistry in the Department of Pathology and Laboratory Medicine at the UVM Medical Center, the assay is routinely and generally used to assess risk of future cardiovascular disease in those populations that are borderline with current risk predictors. The addition of hs-CRP can lead to more aggressive treatment for individuals with higher cardiovascular disease risk, who traditionally would have been followed with a ‘wait and see’ approach. This is just one story of the bench to bedside successes of the LCBR research team.
Division Highlights

Our GI Pathologists: Advancing Cancer Screening

By Rebecca Wilcox, M.D.

Lynch Syndrome, also known as hereditary non-polyposis colorectal cancer or HNPCC, is the most common hereditary colon cancer syndrome, accounting for 3-6% of the total colorectal cancer burden. According to international criteria and recent guidelines for HNPCC diagnosis, screening for Lynch Syndrome should be performed in all newly diagnosed colorectal cancer patients to ensure the proper medical management for the individual patient as well as their relatives. Microsatellite instability (MSI) is a hallmark of HNPCC, and results from the loss of DNA mismatch repair protein function in the cancer cells, which allows the size of DNA microsatellite repeats to change with DNA replication. Patients with MSI have lost the DNA mismatch repair function either due to a germline mutation in one of several DNA mismatch repair genes (e.g., MLH1, MSH2, PMS2, or MSH6), or silencing of one of these genes through hypermethylation of the gene promoter. Patients with MSI due to a germline mutation in one of the DNA mismatch repair genes have Lynch Syndrome. Therefore, to screen for loss of one of the DNA mismatch repair proteins in a patient’s colon cancer, we look for loss of mismatch repair protein expression in the tumor by immunohistochemistry compared to the expression in the adjacent normal epithelium.

Effective October 2014, the GI Pathology team at the University of Vermont Medical Center began performing Universal Screening for Lynch Syndrome on all colon biopsy specimens with colorectal cancer. Although Universal Screening was established at our institution in 2012, we only tested colon cancer resection specimens, and not biopsy specimens. This change to broader screening allows for important clinical decisions to be made prior to surgical resection of the colon cancer. Universal Lynch Screening is a direct partnership with Wendy Mckinnon, M.S., genetic counselor for the University of Vermont Cancer Center Familial Cancer Program.

Welcome & Farewells

WELCOME

Eric Barker-Rose – Cytology Prep Tech
Amy Bourgeois – Resident Program Administrator
Alexandra Cline – Laboratory Assistant
Kristin Day – Pathologist Assistant
Victoria Greenough – Medical Lab Scientist I
Gopal Gurung – Histology Lab Assistant
Ashley Newell, M.S. (ASCP) CM – Point of Care Testing Specialist
Joseph Young, B.S. – Cytology Per Diem Lab Assistant

FACULTY

Julie-Anne Gardner, M.D. – Cytogenetics Pathologist
Laura Schned, M.D. – Per Diem Pathologist
Michelle Yang, M.D. – GI Pathologist
Katie Devitt, M.D. – Heronpathologist
Christina Wessel, Ph.D. – Molecular Epidemiologist

MICROBIOLOGY

Anthony Macuga, M.L.S.
Tyler Sanville, M.L.S.

PHLEBOTOMISTS

Alex Bowen
Ajila Fajic
Amin Hambasick
Whitney Fenton
Hannah Smith
Jed Tague
Logan Volpe

RESEARCH TECHNICIANS

Brian Lynch
Megan McGill
Rebecca Mulheron
Julia Slessova

SPECIMEN RECEIVING

Zac Brown
Cristine Lanoue
Megan Mitchell

FAREWELL

DEPARTURES

Rebecca Merriam-Stelfox – Cytology Prep Tech

Specimen Receiving

Hayley Contois
Vanessa Crain
Paulina Mei
Sam Parker
Dayna Randall

RETIREMENTS

Abdel Elhosseiny, M.D.
Wendy Hurp – Microbiology
Laura Fleming – Pathologist Assistant
Jane Murray – Resident Program Coordinator
Sue O’Brien – Chemistry
Anthony Quinn – Research Technician

UVM Microscopy Imaging Center Outreach

By Douglas Taatjes, Ph.D.

“Project MICRO was wicked awesome!” exclaims one of the students participating in a Project MICRO event held by Jan Schwarz from the Department of Pathology and Laboratory Medicine at the University of Vermont. In 1999, Jan Schwarz and Doug Taatjes, Ph.D., from the UVM Microscopy Imaging Center (MIC) got one of the early Project MICRO Program Kits to “try out” in Vermont, and over the past 16 years, have shared microscopic wonders with over 7,000 children and hundreds of adults.

Project MICRO was developed by the Microscopy Society of America in collaboration with experienced science educators at the Lawrence Hall of Science at the University of California at Berkeley. The goal was to bring microscopes and teaching materials to middle school students nationwide.

For a Project MICRO event, the UVM MIC team sets up a series of activity stations that draw the intrigue and interest of students. The different stations allow students to compare sand samples from different geographic locations, observe a variety of fabrics to determine how each has been made, compare shapes, textures, and colors of flowers and leaves, study structures of dried insects, and explore the minute inhabitants of pond water. “Who knew that all those tiny animals could live inside a few drops of water?” At the conclusion of each microscopic festival, the teachers are given activities for their classes to continue their explorations.

We are opening the door to science through visually exciting exploration of the microscopic world. Many thanks to Jan and her team for developing our future scientists in Vermont! If you are interested in having Project MICRO at your child’s school, contact Jan Schwarz at janet.schwarz@med.uvm.edu.”
New & Notable

Promotions

MARLEM AYALA to Laboratory Assistant II
MARK FUNG, M.D., Ph.D., to Professor
ANDREW GOODWIN, M.D., to Associate Professor
MICHAEL LEWIS, M.D., to Laboratory Medicine Division Chief as of October 1, 2015

LISA MALLABAR went through basic Specimen Receiving Program and was promoted to Laboratory Assistant II.

REBECCA WILCOX, M.D., to Associate Professor

Awards/Recognition

DEBORAH COOK, M.D., was appointed Connections Course Director
DON DUKETTE received the UVMC Vision Award
LIN KRISTIANSEN, M.T. (ASCP) received the Mary Breen Award

DEBRA LEONARD, M.D., Ph.D., will receive the College of American Pathologists’ Lifetime Achievement Award at the annual meeting in Nashville, Tenn., in October 2015

REBECCA WILCOX, M.D., and TAMARA WILLIAMS, Ph.D., were named UVM College of Medicine 2015 Frymoyer Scholars

CHRISTINA WOJEWODA, M.D., was chosen as one of ASCP’s 40 Under 40

Research News

KELLY BUTNOR, M.D.


DEBORAH COOK, M.D.

JAMES DEKAY, M.D.
and
MARYAM ZENALI, M.D.

MARGARET DOYLE, PH.D.
Recent findings of long-chain n-3 polyunsaturated fatty acids (LCn-3 PUfAs) on atherosclerosis and coronary heart disease (CHD) contrasting studies in Western countries to Japan. Sekiawka A, Doyle MF, Kuller LH. Trends Cardiovasc Med. 2015 Mar 6 pii: S1050-1738(15)00074-2. doi: 10.1016/j.tcm.2015.03.001.

ARTI SHUKLA, PH.D.

NIKOLETTA SIDIROPOULOS, M.D., PH.D.

MARK EVANS, PH.D.

MARK FUNG, M.D., PH.D.


DEBRA LEONARD, M.D., PH.D.

NANCY SWORDS-JENNY, PH.D.


DOUGLAS TAATJES, PH.D.

RUSSELL TRACY, PH.D.


SUZANNE TUCKER, M.D.

Publications

WHO KNEW?

MISS VERMONT, ALAYNA WESTCOM, is a Medical Laboratory Scientist in the Department of Pathology and Laboratory Medicine at the University of Vermont Medical Center. Her platform is success through science, technology, engineering and mathematics (STEM) and she brought that all the way to the Miss America pageant, a leading national scholarship program for young women. In her spare time, between two jobs and representing Vermont, American Pathologists’ Lifetime Achievement Award at the annual meeting in Nashville, Tenn., in October 2015.

REBECCA WILCOX, M.D., and TAMARA WILLIAMS, Ph.D., were named UVM College of Medicine 2015 Frymoyer Scholars.
### Research News

**BRENDA WATERS, M.D.**


**DONALD WEAVER, M.D.**


### Glutaredoxin Patents for Treatment of Pulmonary Fibrosis

In 2014, **YVONNE JANSEN-HEININGER, Ph.D.**, a Professor in the Department who works in the area of Redox Biology and Pathology, received two patents developed through her research on glutaredoxin. Dr. Janssen-Heininger and her team, including Assistant Professor **VIKAS ANATHY, Ph.D.**, discovered and patented the use of this oxidant-controlling enzyme as a treatment for patients with lung fibrosis and other diseases. The second patent covers a new method to detect certain forms of oxidized proteins in tissues, which has potential diagnostic utility. These patented discoveries are being further developed for clinical use through a new R43/44 SBR Fast Track I/II grant in collaboration with Celdara Medical entitled: “Preclinical development of inhalable glutaredoxin-1 for the treatment of PF.” The goals of this study are to develop a dry powder formulation of mammalian glutaredoxin-1 (Grx1), an enzyme implicated in pulmonary fibrosis; to confirm the efficacy of the murine variant in murine models of pulmonary fibrosis; and to complete IND-enabling GLP safety and toxicity studies for the human Grx1 dry powder particles (ultimate clinical product) in rats and monkeys.

### New Grants in 2014 – 2015

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Project Title</th>
<th>Sponsor Name</th>
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</thead>
<tbody>
<tr>
<td>Vikas Anathy, Ph.D.</td>
<td>Endoplasmic Reticulum Stress Signaling in Allergen-induced Airway Remodeling</td>
<td>Asthma and Allergy Foundation of America</td>
</tr>
<tr>
<td>Vikas Anathy, Ph.D.</td>
<td>Endoplasmic Reticulum Stress Signaling in Allergen-induced Airway Remodeling</td>
<td>National Heart, Lung, and Blood Institute/NIH/DHHS</td>
</tr>
<tr>
<td>Vikas Anathy, Ph.D.</td>
<td>Influenza Virus Hijacks Host Cell Unfolded Protein Response</td>
<td>Francis (Parker B.) Foundation</td>
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<tr>
<td>Mark Evans, Ph.D.</td>
<td>In Situ Hybridization Signal Patterns as Markers of Cervical Neoplasia Grade and Lesion Progression</td>
<td>VCC/LCCRO Pilot Award</td>
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<td>Yvonne Janssen-Heininger, Ph.D.</td>
<td>Evaluation of the Impact of 9, 10-Mixed Isomer of CXA-10 on Existing Pulmonary Fibrosis</td>
<td>Complexa, Inc.</td>
</tr>
<tr>
<td>Nancy Jenny, Ph.D.</td>
<td>Defining a Comprehensive Reference Profile of Circulating Human Extracellular DNA</td>
<td>University of California, San Francisco</td>
</tr>
<tr>
<td>Nancy Jenny, Ph.D.</td>
<td>Mediators of Atherosclerosis in South Asians in America</td>
<td>University of California, San Francisco</td>
</tr>
<tr>
<td>David McMillan, Ph.D.</td>
<td>GSTP1-Mediated Fas S-Glutathionylation, Apoptosis and Lung Fibrosis</td>
<td>National Heart, Lung, and Blood Institute/NIH/DHHS</td>
</tr>
<tr>
<td>Arti Shukla, Ph.D.</td>
<td>Exosomes in Development and Therapy of Malignant Mesothelioma</td>
<td>Department of Defense</td>
</tr>
<tr>
<td>Russell Tracy, Ph.D.</td>
<td>Cardiovascular Health Study (CHS) – Core Support Renewal</td>
<td>University of Washington</td>
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<tr>
<td>Russell Tracy, Ph.D.</td>
<td>Immune Function and the Risk of CVD among HIV Infected and Uninfected Veterans</td>
<td>Vanderbilt University</td>
</tr>
<tr>
<td>Russell Tracy, Ph.D.</td>
<td>JHS/AHA Cardiovascular Genome Phenome Study</td>
<td>University of Mississippi Medical Center</td>
</tr>
<tr>
<td>Russell Tracy, Ph.D.</td>
<td>Role of innate Immunity in HIV Related Vascular Disease: Biomarkers and Mechanisms</td>
<td>Albert Einstein College of Medicine at Yeshiva University</td>
</tr>
<tr>
<td>Russell Tracy, Ph.D.</td>
<td>T-cell Subsets as Risk Factors for CVD in CHS and MESA</td>
<td>University of Washington</td>
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<tr>
<td>Russell Tracy, Ph.D.</td>
<td>Targeting Hypercoagulation to reduce Inflammation in Treated HIV Disease</td>
<td>Minneapolis Foundation</td>
</tr>
<tr>
<td>Adrianus van der Velden, Ph.D.</td>
<td>Investigation of the Pathophysiologic Associations of GSTP1 in Emphysema and Lung Cancer</td>
<td>VCC/LCCRO Pilot Award</td>
</tr>
<tr>
<td>Jill Warrington, M.D., Ph.D.</td>
<td>Reducing Unnecessary Laboratory Testing in Low-risk Surgical Candidates</td>
<td>Vermont Medical Society (VMS) Education and Research Foundation, Inc.</td>
</tr>
</tbody>
</table>
Clinical News

The Future of Medicine: How Precision Medicine is Revolutionizing Healthcare

Less than a decade ago, Genomic Medicine was an aspirational concept in the health care community. Today, we are planning a Genomic Medicine Program at the University of Vermont Medical Center. While there has been an explosion of genomics in the research realm, genomic technologies are crossing over into clinical applications. Next generation sequencing (NGS) technology can be considered a fundamental technology permitting scalable genomic testing in the clinical laboratory. While the Department is awaiting submission and approval of a Certificate of Need for the proposed Genomic Medicine Program, the Molecular Pathology Laboratory of the Department is validating a custom-designed targeted gene panel for solid tumors that will be performed using NGS technology. The molecular pathology team is diligently working on building and instituting this new technology and the cancer care pathway to ensure the appropriate use of this new testing by the Fall of 2015.

Nikoletta Sidiropoulos, M.D.
Director of Molecular Pathology

From the Lab: the UVM Medical Center Clinical Laboratory Receives Accreditation from College of American Pathologists

We are proud to share that the Department of Pathology and Laboratory Medicine received re-accreditation in September 2014 from the College of American Pathologists (CAP). CAP accreditation is considered one of the best and most rigorous CLIA accreditation pathways. Twelve inspectors spent two days performing the inspection, and in their summary, they offered many positive comments about our clinical laboratories. Seventy to eighty percent of all diagnoses and decisions in medicine rely on laboratory results. Approximately 2.7 million clinical laboratory tests are performed at the University of Vermont Medical Center each year. From the time a medical provider orders a test, many steps must occur quickly and properly to ensure the result is accurate and timely. Our Laboratory exceeds the standards set by numerous accrediting agencies. Our committed staff members are dedicated to providing accurate and timely test results that contribute to the health and well-being of all the patients our laboratory serves.

Andrew Goodwin, M.D.
Director of Coagulation

Nonconforming Event Management at UVMMC—January 2015

What is a nonconforming event (NCE)? As the phrase suggests, NCEs are events that do not follow established procedures or applicable regulatory requirements. NCEs have the potential to affect patient safety or the efficiency and effectiveness of workflow or operations. In February 2014, we established an NCE management program as part of our Quality Management System. Any event that deviates from established protocols is documented electronically. Entries are categorized by event location, type of event, and severity. Tracking and reviewing NCEs allows us to focus our resources on issues that have the greatest impact on improving patient care. Process improvement to remove the cause of NCEs leads to improved quality and patient safety.

Nicole Carnay, MT, (ASCP) M.S.
Clinical Laboratory Quality Officer

Test Utilization Review Update

As of September 2014, Pathology and Laboratory Medicine residents began reviewing orders for referral tests that cost more than $500 per test. Previously, these expensive tests have not been reviewed. The new review process will support resident education as well as optimize test utilization efforts within the UVM Medical Center. Residents may contact the ordering provider with questions on the purpose of the ordered test or suggestions for alternative testing algorithms. This initiative will encourage referral laboratory testing in an outpatient setting. Testing of unstable specimens will not be delayed by this process.

Christina Wojewoda, M.D.
Director of Microbiology
Graduating Residents and Fellows

Congratulations to our graduating class of residents and fellows. All six of our graduating residents are pursuing subspecialty fellowships.

Residents

KOSSIVI DANTEY, M.D., Soft Tissue Fellowship and Cytopathology Fellowship, University of Pittsburgh Medical Center

JAMES DEKAY, M.D., Dermatopathology Fellowship, University of Vermont Medical Center

TRICIA MURDOCK, M.D., Gynecologic Pathology Fellowship, Johns Hopkins University

DANIEL OLSSEN, M.D., Molecular Genetic Pathology Fellowship and Breast Pathology Fellowship, Mayo Clinic

KANAYO TATSUMI, M.D., Forensic Pathology Fellowship, Office of Chief Medical Examiner (OCME), City of New York Department of Health and Mental Hygiene

KIRSTEN THRELKELD, M.D., Cytopathology Fellowship, University of Vermont Medical Center

Fellows

MARY GUPTA, M.D., Surgical Pathology, Assistant Professor of Medical Education, University of Tennessee Health Science Center College of Medicine in Memphis, TN

SARA BROWNCHILDE, M.D., Cytopathology Fellow, Eastern Great Lakes Pathology in Buffalo, NY

GRETCHEN FRIELING, M.D., Dermatopathology Fellow in Boston, MA

New Residents

Our new residents are joining our department from across the country. A special welcome to:

PRAJESH ADHIKARI, M.D., University of Cincinnati College of Medicine

ELAINE AMORESANO, M.D., Rutgers New Jersey Medical School

RYAN COATES, M.D., University of Utah School of Medicine

ANDREW LAMAR, M.D., University of Oklahoma College of Medicine

UVM Pathology Student Fellowship

The pathology student fellowship program is entering its 59th year. IAN MCDANIELS recently completed his fellowship year and LAURIE GRIESINGER and RICHARD SMITH are our two new student fellows.

Graduate Students

JAMES D. NOLIN completed his Ph.D. degree with YVONNE JANSEN-HEININGER, Ph.D. He will be starting his post-doctoral fellowship at the University of Washington, Seattle.

VIKAS ANATHY, Ph.D.

Nicolas Chamberlain (1st year)

YVONNE JANSEN-HEININGER, Ph.D.

Shi Biao Chia (Wyatt) (1st year)

ARTI SHUKLA, Ph.D.

Phillip Munson (1st year)

Joyce Thompson (4th year)

ALBERT VAN DER VLIET, Ph.D.

Christopher Dustin (1st year)

Robert Bauer (3rd year)

Andrew Little (3rd year)

Faculty Continuing Education

ANDREW GOODWIN, M.D., successfully completed the MBP Advanced Practical Breast Pathology Program sponsored by the CAP.

VALERIE ROGERS, M.T. (ASCP) received her M.S in Healthcare Management from Champlain College in May 2015.

The University of Vermont Pathology Student Fellowship has a very long and rich history. The fellowship was started in 1956 by the Department Chair, Robert Coon, M.D., and has had over 120 fellows in the past 59 years. With the changing economics of healthcare and medical schools, we wanted to assure the sustainability of our Pathology Student Fellowship Program for years to come. Working closely with Meredith Armitage from the University of Vermont Foundation, we have established the Pathology Student Fellowship Endowment fund to support two to three student fellows for years to come. One very generous gift of $200K was from our own Emeritus Professor, William Pendlebury, M.D., and one of the student fellows each year will be named the William Ward Pendlebury Fellow. With the gifts to date, the endowment is over $500,000 and continuing to grow with a goal of $2M total endowment.

John Lunde, M.D. (left) and William Pendlebury, M.D. (right) at the Pathology Student Fellowship Endowment kickoff celebration.
Meet the PHYSICIAN-SCIENTIST

In March 2015, a study by DONALD WEAVER, M.D., entitled “Diagnostic Concordance Among Pathologists Interpreting Breast Biopsy Specimens,” was published in The Journal of American Medical Association and was a featured topic on WCAX’s program “The :30.” The study, comparing the consensus diagnosis of a panel of expert breast pathologists to that of 115 pathologists around the country, demonstrated that pathologists who review the same breast biopsy provide different diagnoses in certain cases. While the accuracy of an invasive carcinoma diagnosis is around 97% and accuracy of breast biopsies overall is 93%, in cases of atypical hyperplasia the agreement was only 48%, and the reproducibility of ductal carcinoma in situ was around 80%. This study highlights the need for more research on mechanisms to improve the consensus diagnosis of atypical hyperplasia, and cautions against pursuing aggressive treatment for atypical hyperplasia without a second opinion.