ARUP’s Culture of Innovation

Because ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology, it has grown organically through client relationships rather than through acquisitions. ARUP’s business model and test-development efforts are driven by medical necessity and innovation rather than short-term financial gains.

ARUP has funded and continues to fund various initiatives to adapt emerging technologies to laboratory medicine. Bridging the gap between research and application can be difficult, but ARUP maximizes the use of new advances.

Not only are new tools implemented at ARUP for diagnostic tests, but ARUP methods are actively shared with the world through scientific publications, presentations, open-source databases, free multi-media based education, and technology licenses.
Mass Spectrometry

In its decade-long focus, ARUP has made mass spectrometry mainstream in laboratory medicine where chromatography once dominated. The higher sensitivity and specificity of mass spectrometry are uniquely suited for clinical analyses of small biological molecules, drugs, metabolites, and even microorganisms and sugar moieties. Many of these projects have had a significant positive impact on the quality and cost-effectiveness of patient care.

Methylmalonic Acid (MMA)—one of ARUP’s newest inventions

One of ARUP’s earlier inventions was a mass spectrometry-based MMA test to detect vitamin B12 deficiency in patients. Today, ARUP’s method is used by major commercial laboratories and is available to others through a non-exclusive license. More than 20 million MMA assays are performed each year in the United States.

State Newborn Screening—ARUP’s contribution to Utah’s most vulnerable citizens

In 2003, ARUP purchased rights to a mass spectrometry method that allows simultaneous analysis of multiple newborn diseases. At the time, newborns in Utah were screened for only four diseases. ARUP approached the Department of Health, funded a year-long pilot program, actively lobbied with insurers and legislatures, and facilitated the expansion of newborn screening under state law.

ARUP donated $750,000 to fund the start-up and pilot phases of the state program, with the University of Utah as the pilot site. Thanks to ARUP’s mass spectrometry test, Utah newborns are now screened for more than 40 diseases.

Microbiology and Glycobiology—new directions

ARUP is developing tests that utilize time-of-flight mass spectrometry for classification of clinical isolates of bacterial and fungal species to reduce testing costs. Mass spectrometry is used to analyze sugar moieties to diagnose patients with lysozomal storage disorders. This is the first time mass spectrometry has been used in glycobiology in lab medicine.
ARUP’s mass spectrometry projects have had a significant impact on the quality and cost-effectiveness of patient care.
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**HotSpot Algorithm Program**

Developed by ARUP’s medical director Dr. Frederick G. Strathmann, HotSpot is an automated quality tool used to monitor the risk of well-to-well contamination in liquid chromatography tandem mass spectrometry assays.

ARUP recognized a heightened risk of false-positive LC-MS/MS-based confirmation testing conducted in 96-well plates. HotSpot was developed to effectively monitor and mitigate the risk of reporting false-positive results.

Prior to the implementation of the HotSpot software program, technologists manually identified elevated samples above a laboratory-set threshold. This manual process made use of a repeated, sequential numbering system for each well in a given 96-well plate; it was time-consuming and required extensive analysis of the data, as well as a working knowledge of laboratory thresholds.

The HotSpot software program generates a graphical layout of the 96-well plates from the exported, raw data without the need for review or manipulation by a technologist. HotSpot allows instant visual confirmation of internal standard deviation and samples at risk of falsely elevated results due to contamination in a matter of seconds, and decreases the contamination rate due to human error.

“ARUP is always striving for advancement in both technology and quality. The HotSpot program is one example of the widespread effort to implement novel electronic tools as needed to maintain the necessary and expected level of quality assurance.”

Dr. Strathmann
Approximately 250 clinical specimens are sequenced daily at ARUP and reported back to clinicians. Infectious diseases in which viruses mutate under therapeutic pressure and give rise to strains that are resistant to treatment are monitored.

Similarly in oncology, ARUP uses sequencing tools to determine innate or acquired mutations that make cancer cells either responsive or resistant to drugs. Clinical DNA sequencing plays an essential role in treatment decision making, and new sequencing tools have become necessary to further fine-tune therapy at the individual level in a cost-effective manner.

**A Clinical Mutation Database—enabling interpretation of genetic data**

With the accumulation of DNA-sequencing data, ARUP needs to curate databases targeted to the treatment of patients. Academic databases have limited usefulness in that they merely archive mutations without adequate clinical validation of each entry. Through an ARUP and University of Utah Department of Pathology initiative, the ARUP Disease Database was created in 2010 and now hosts fully curated, clinically validated mutations for nine diseases at [www.arup.utah.edu](http://www.arup.utah.edu).

This open-source database is accessed by more than 100 professionals daily; it receives submissions on clinically observed new mutations and is used by many institutions to interpret data that is generated by clinical sequencing.

**Next-Generation Sequencing—academic collaboration**

In the ever-evolving world of next-generation sequencing (NGS), ARUP launched its first set of clinical tests in 2012. ARUP actively collaborates with clinicians who are eager to find causative genes for their patients using NGS. Out of this endeavor, ARUP is emerging as a clinical center of excellence for immunogenetic disorders and a destination hub for research-based exome sequencing for clinicians who are interested in identifying disease-causing gene mutations.
Clinical DNA sequencing plays an essential role in treatment decision making; new sequencing tools have become necessary to further fine-tune therapy at the individual level in a cost-effective manner.
Digital Pathology Initiative

In its mission to train future anatomic pathologists, ARUP has established the digital pathology initiative, which is supported by an ever-growing digital archive library. Cytopathology and hematopathology case reports that utilize digital slides are provided at no cost for continuing education credits at www.arup.utah.edu.

A recent invention by ARUP’s medical director Dr. Mohamed Salama is an informatics tool that automates scanning for tissue fibrosis on slides. Automated fibrosis scanning is a service that ARUP offers at minimum cost to its academic and industry collaborators.

Immunohistochemistry Core

ARUP funds an immunohistochemistry core facility to develop new antibodies useful to anatomic pathology tests. This facility is also a center for collaborative research and for the national Children’s Oncology Group, and is funded by grants obtained by ARUP’s chief medical officer and director of laboratories Dr. Sherrie Perkins.

ARUP funds an immunohistochemistry core facility to develop new antibodies useful to anatomic pathology tests.
Innovation Incubators

ARUP has served as an incubator for some of Utah’s successful small businesses. These successes are attributed to ARUP’s willingness to partner with companies and provide the much-needed real-world context to commercial technology development.

Dr. Carl Wittwer and the LightCycler

In 1988, Dr. Carl Wittwer became an assistant professor at the University of Utah Department of Pathology and started a research project that would involve integrating new technology into clinical practice.

Dr. Wittwer came up with the idea of using hot air and capillary tubes to perform PCR. It was an idea that has grown into a major clinical assay system. Using his expertise in enzyme kinetics and fluorescence-detection methodology, Dr. Wittwer invented the LightCycler, a machine for extremely rapid PCR that can be monitored in real time. The LightCycler is currently sold worldwide by Roche Molecular Biochemicals, based in Switzerland.

This instrument is the basis of a number of new diagnostic tests that promise to greatly increase the speed of genetic testing as well as dramatically reduce assay costs.

“If I were in any department other than pathology, my instruments would never have been made,” says Dr. Wittwer, medical director and technical vice president of the Advanced Technology Group and the General Flow Cytometry Laboratory. “As a pathologist, I recognized a clinical need. Because I was located within a cutting-edge research environment, I had access to the basic techniques I needed.”

Avansci Bio

A more recent startup company also owes its roots and current success to ARUP. ARUP’s medical director Dr. Katherine Geiersbach identified the need for an automated device to dissect slide-mounted tissue specimens. The device had to work in the context of diagnostic workflow and economy requirements at ARUP (which also apply to other diagnostic laboratories).

The R&D group at ARUP funded Dr. Geiersbach’s endeavor and provided machine shop support for building the initial prototype. The company is now able to produce and market these devices. ARUP continues to fund Dr. Geiersbach’s research in molecular oncology.
“If I were in any department other than pathology, my instruments would never have been made,” says Dr. Wittwer. “As a pathologist, I recognized a clinical need. Because I was located within a cutting-edge research environment, I had access to the basic techniques I needed.”
Personalized Medicine

Using granular test data to direct individualized therapy is not new to ARUP. However, ARUP is the only major laboratory that routinely practices personalized medicine through its diagnostic testing services. ARUP tests include those that guide cancer therapy based on genetic biomarkers specific to the patient and those that identify resistance of a viral strain against drugs, as well as therapeutic drug monitoring, pharmacogenetic testing, and companion diagnostics that integrate drug development and laboratory medicine. ARUP is a destination laboratory for many industry and academic collaborations in the field of personalized medicine.

Dr. Elaine Lyon has championed personalized medicine and its role in improving patient care through improved diagnosis and management of disease. Dr. Lyon has testified before the United States Special Committee on Aging during a Genetic Testing Roundtable discussion regarding the importance of personalized medicine in the arena of genetic testing.
**Warfarin Genotyping**

ARUP developed a software tool that guides clinicians to better manage therapy with the anticoagulant warfarin (Coumadin) using genotype and other patient demographics. ARUP’s medical director Dr. Gwen McMillin recognized that while warfarin is the poster-child for personalize medicine, in practice, genotype data was not used by clinicians because it was complicated to interpret; a tool was needed to bridge that gap.

ARUP invested in the creation of a dynamic software tool, PerMIT:Warfarin, partnering with PGxL, a startup company at the University of Louisville. ARUP also funded the prospective clinical trial at the University of Utah Orthopedic Center.

Patients who were enrolled in the software-guided arm achieved steady-state drug levels three days earlier than the standard-of-care arm, allowing these patients to be discharged earlier.

Based on this success, the University of Utah Orthopedic Center has become the trial site for at least three other NIH-funded warfarin studies in which ARUP is the lead contributor.
Companion Diagnostics—innovative partnerships with pharma

ARUP often partners with pharmaceutical companies to collaborate in drug trials or post-market diligence. ARUP may perform laboratory testing for patients enrolled in the trials or to obtain FDA clearance for diagnostic tests that are indicated by certain drugs.

A growing number of cancer drugs require companion diagnostic testing, which either qualifies patients to receive the drug or excludes them due to a lack of response or adverse reactions.

In order for pharmaceutical companies to co-market the test and the drug, both need to be FDA-cleared. ARUP is seen as a premier facility that can stand up to the quality requirements of the FDA.
A growing number of cancer drugs require companion diagnostic testing.
"I feel very fortunate that ARUP’s executive team recognized that automation would enable us to keep up with growth and improve our quality and performance, and that I was given the freedom to think outside the box and find unique solutions to unique problems. My colleagues at ARUP have also added to my ideas, resulting in systems that work well and achieve our objectives."

Dr. Charles Hawker
**Automation**

ARUP is one of the most automated laboratories in the United States. An 1,100-foot transport and sorting system with a capacity of 8,000 specimens per hour is one of the key elements. Equally important are two automated sorters that load finished specimens into storage trays and a two-story automated storage and retrieval system (AS/RS), which is housed in the world’s largest clinical laboratory freezer. The AS/RS capacity exceeds 2.3 million specimens, and individual specimens are robotically retrieved in less than 2.5 minutes.

ARUP has also installed the world’s first automated thawing/mixing workcell, which thaws and mixes frozen specimens on the transport system at a rate of more than 1,000 per hour, thus reducing pre-analytical preparation time. ARUP is committed to developing superior automation that improves the overall quality of testing and reduces turnaround time.

The key to ARUP’s automation success lies in additional changes that were implemented in conjunction with automation: the adoption of a standardized transfer tube, the consolidation of higher-volume testing in the Automated Core Laboratory, the development of a new rules-based, intelligent order-entry and support software system (Expert Specimen Processing or ESP), and the redesign of the specimen processing workstations to be used with the automated transport and sorting system.

While re-engineered its various processes, ARUP utilized the internal continuous quality-improvement program, which uses employee teams to recognize and address improvement opportunities. ARUP has achieved a superior overall outcome that has been successful not only from ARUP’s perspective but from the perspective of ARUP’s clients as well.
Utilization Management—more than testing results

**ATOP®**

As a medical business, ARUP believes that our focus should be on patient care, not on generating profit. Thus, the patient and the patient’s hospital are more important to ARUP than the revenue we receive.

Ten years ago, ARUP established a process called ATOP, Analyzing Test Ordering Patterns™. ARUP clients receive ATOP reports that encourage them to utilize less, not more, of our services.

ARUP’s ATOP report identifies potential over-, under-, and misuse of individual laboratory tests. The report assesses the clinical and economic impact of suboptimal test ordering, and the insights gained from an ATOP report can be used to improve patient care, increase efficiency, and reduce costs.

In 2009, ATOP won the Award of Excellence in the Technical Publications Category from the Society for Technical Communications.

**ARUP Insource Advantage™**

ARUP Insource Advantage evaluates the economic feasibility of performing specific tests in-house vs. sending these same tests to a reference laboratory partner. Offering this unique cost-accounting tool to clients at no cost, ARUP provides both information and data, focusing on high-volume and high-cost spending to facilitate make vs. buy decisions. The ARUP Insource Advantage report analyzes
current and historical costs as well as volume information to assist ARUP clients in managing their send-out purchase services in the most financially feasible way.

For example, by partnering with ARUP, the University of Rochester Medical Center (URMC) was able to educate its physicians, control overutilization, and save nearly $30,000 a month in send-out expenses. To read the full article, which appeared in the March 2012 issue of CAP Today, visit: http://tinyurl.com/c5x9vq7.

**ARUP Consult®**

ARUP Consult, The Physician’s Guide to Laboratory Test Selection and Interpretation, is a dynamic reference tool, available in web, mobile, and app formats, provided by ARUP for all physicians and clinicians at no cost or obligation. ARUP Consult’s goal is to assist the clinician with test selection and interpretation, since knowing the right test to order for a specific disease can improve patient care and decrease unnecessary testing and costs.

In 2008, Consult won the Award of Excellence in the Online Competition Category from the Society for Technical Communications. Consult was also a 2008 Computerworld Honors Program Laureate in the Healthcare Category. The Computerworld Honors Program focuses on companies and entities who utilize innovative technology to benefit society.

**ARUP Gateway™**

An innovative web-based tool, Gateway won the eHealthcare Leadership Gold Award for Best Care/Disease Management site in 2009. Gateway allows ARUP clients to seamlessly integrate their test menu with ARUP’s, allowing for up-to-date test data and real-time changes. Clients can brand their organization’s Gateway site with a customized look and feel and have complete administrative control of the site and data. Gateway provides clients with a cost-efficient alternative to expensive in-house development options and outside web consultants.
ATOP won the Award of Excellence in the Technical Publications Category from the Society for Technical Communications.

Consult won the Award of Excellence in the Online Competition Category from the Society for Technical Communications.

Consult was a Computerworld Honors Program Laureate in the Healthcare Category.

Gateway won the eHealthcare Leadership Gold Award for Best Care/Disease Management site.
ARUP Genetic Counselors

ARUP genetic counselors collectively save ordering institutions more than $30,000 per month by modifying test orders to improve utilization. ARUP genetic counselors consider the clinical utility and cost-effectiveness of the ordered tests and contact the ordering institution and/or healthcare provider to collect additional clinical information, confirm testing, or suggest alternative testing based on the provided clinical information or family history.

Genetic counselors assist in an average of 107 test modifications per month, for an average monthly cost-savings of $36,451 from cancellation of misordered tests.

The misordering of genetic tests is a common occurrence in diagnostic laboratories. ARUP Laboratories’ genetic test cancellations and additions have enabled ARUP to understand which tests are most commonly misordered and to implement changes in procedures.
ARUP and Physician Office Business

ARUP used to market to hospital laboratories and physician offices. The physician office business did well, but ARUP realized that it should not compete with its clients, who offer routine testing for local physicians.

The volume from physician offices was low compared to the business from hospital laboratories, and physician offices were outside ARUP’s core mission of being a regional and national reference laboratory to medical facilities. ARUP wanted to support clients’ efforts in their local communities.

In alignment with ARUP’s core business philosophy of putting the patients first, ARUP’s belief is that testing is best performed close to the patient. ARUP no longer competes with clients for physician office business. Instead, ARUP supports clients by helping them bring certain testing in-house.

Rather than competing with its clients for physician office business, ARUP chooses instead to support clients’ existing test menus by offering highly complex and unique lab tests, with accompanying consultative support, to enhance clients’ abilities to provide laboratory services.
Research and Development

The ARUP Institute for Clinical and Experimental Pathology®, the research arm of ARUP, sponsors projects within four broad categories: creating new laboratory tests; improving current clinical laboratory tests; evaluating and critiquing tests, including alpha- and beta-site protocols; and conducting basic and clinical research projects.

By using the research expertise of university-based scientists, as well as the resources and acumen of ARUP institute staff, institute projects have been extremely effective in expanding the quantity, quality, efficiency, and sophistication of laboratory tests.

Since its inception, the institute has developed more than 600 tests that ARUP now performs in-house. Of these tests, more than 400 were developed by institute scientists, while more than 200 others were improved and validated so that ARUP could perform them in-house rather than continue to refer them out. ARUP research scientists have shared their knowledge, experience, and new developments with the scientific community by publishing more than 1,600 original peer-reviewed research publications in leading journals.

The institute strives for a smooth translation of basic research into applied science and clinical assays. This focused approach and responsiveness have led to new assays in all areas of laboratory medicine. Novel assays have been developed for employing multianalyte technology to determine immune and inflammatory responses, as well as for vitamin and nutritional status, tumor markers, therapeutic drug monitoring, and autoimmune/allergy evaluation.

The institute has also facilitated the introduction of new instrumentation and approaches for analyzing genetic diseases and the metabolic and immune status of patients.

Institute research projects are directed by departmental faculty members in conjunction with institute research scientists. Research proposals and progress are reviewed biannually. This unique combination of investigator-initiated, goal-oriented research has proven to be extremely effective in bringing new tests to market and improving existing assays, with the end result of improved patient care.
| # in-house tests developed by the institute | 600 |
| # developed by institute scientists | 400 |
| # improved and validated | 200 |

The institute’s mission is to be at the forefront of innovative research and development in clinical laboratory medicine.