WhitePaper

How Clinical Laboratories and Pathology Groups Can Succeed in Pharmacogenomics

What the Experts are Saying

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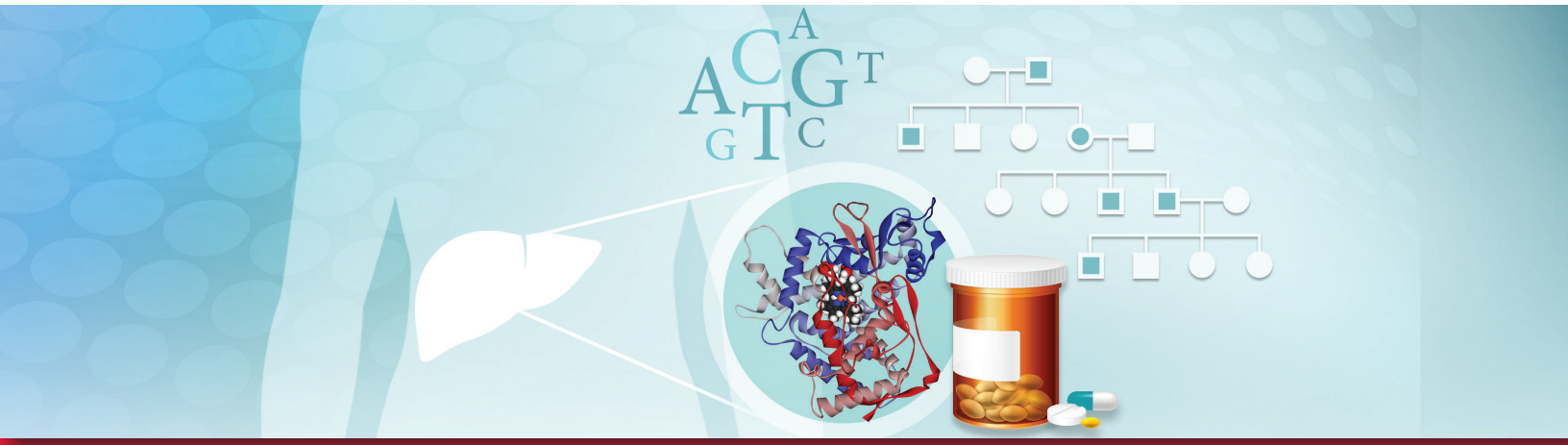

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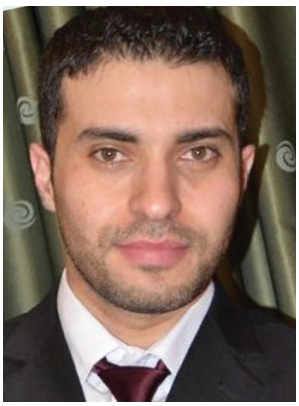
Introduction

Increasing understanding of the genetic basis of an individual's response to drugs, including how and how quickly a drug is metabolized (pharmacodynamics and pharmacokinetics), has opened the door to an increasingly personalized approach to drug prescription. Among the examples are the genes that code for the cytochrome P450 family of enzymes, associated with individual variations in drug metabolism.[1] By identifying drugs most likely to benefit a patient, assessing likely dose response, potentially avoiding adverse reactions and reducing unnecessary use of drugs, pharmacogenomics testing (PgX) can help optimize treatment and reduce costs associated with complications or inappropriate utilization. As research demonstrating its clinical utility and associated health economics benefit continues[3,4] and with the trend toward value-based healthcare, PgX is on the path to becoming the standard of care. Already, more than 150 FDA-approved drugs include pharmacogenomics information in their labeling.[5] This demand for PgX presents an opportunity for clinical labs, many of which have successfully launched PgX services over the last two or three years and enjoyed robust growth.

The following is based on insights gleaned from an expert panel of lab directors and consultants at leading labs as they discussed industry trends, best practices and guidance for labs looking to tap into the opportunities in PgX.

Meet the Expert Panel



Tariq Adwan, PhD, Director of Research and Development, Alpha Genomix Laboratories, graduated with honors from Misericordia University with a BS in biology and chemistry. He received his PhD from the University of Colorado's program of Cell Biology, Stem Cells and Development, where he also did his postdoctoral fellowship. His research focused on understanding the molecular mechanism underlying salivary gland dysfunction in head and neck cancer patients. Dr. Adwan is a co-author on a number of peer-reviewed publications and has been invited to present his work at scientific meetings, including the Federation of American Societies for Experimental Biology Conference on Lipid Mediated Signaling in Cancer.

Kristine Ashcraft, CEO, Genelex Corporation, defines the company's overall strategy, vision and place in the pharmacogenetics industry. She is responsible for business development, product design, market share and internal systems, in addition to being the primary liaison for governmental agencies, clients and partners. Prior to joining Genelex, Ms. Ashcraft worked in sales management at an insurance provider and served in management roles in the nonprofit sector. She obtained her MBA in entrepreneurship, graduating magna cum laude from the Franklin W. Olin Graduate School of Business at Babson College, and BS in molecular biology from the University of New Haven.

Weike Mo, PhD, FACB, Technical Director, Molecular Testing Labs, has built and managed both multidisciplinary R&D and clinical testing teams. His experience includes assay development for clinical diagnostics (molecular genetics, ELISA/EIA and LC-MS/MS) and implementation of a lab automation system for a genetics lab that performs more than 20,000 PCR reactions daily and a toxicology lab that tests 40,000 urine drugs daily. He received his PhD in cell and development biology from Oregon Health and Sciences University and BS in biotechnology from Tsinghua University, Beijing, China.

Bradley A. Moss, President, Patients Choice Laboratories, oversees business development, health economics, strategic partnerships and related activities within the company. Previously, he served as the Chief Business Officer for SeKayi Management, a $10M healthcare management organization, where he oversaw three subsidiaries managing more than 500,000 patients in four states. Prior to that, he was National Director of Sales for DailyMed Pharmacy, a subsidiary of Arcadia Resources, Inc. Mr. Moss received his BS from Eastern Illinois University and his MBA from the University of Illinois.

Bronwyn Ramey-Hartung, PhD, CEO, Phoenix Laboratory Consulting, has more than 15 years of laboratory experience in academic and clinical laboratories, where her work focused on molecular genetics assay design, validation and troubleshooting, as well as raw data analysis, phenotype interpretation and reporting. Her pharmacogenetic specialties include CYP450 haplotyping and copy number analysis. Dr. Ramey-Hartung also has experience in the development and quality systems management of LIMS, translational reporting and medical device software. She received her PhD in microbiology and biochemistry from Indiana University Bloomington and BS in biology from Trinity University.

Liz Thompson, MB (ASCP), COO, Clinical Lab Consulting, LLC, came to CLC from a large molecular diagnostics laboratory, where she managed the Laboratory Quality Assurance Department for Molecular Genetics, Toxicology and Infectious Disease. Her previous experience includes managing an HLA laboratory that focused on tissue typing for bone marrow transplant patients. She was published in Tissue Antigens and Human Immunology during this time. Liz graduated in 2006 with a BA in biology from Lewis & Clark.

What follows are the insights of these distinguished panelists as they discuss industry trends, best practices and guidance for clinical labs and pathology groups looking to tap into the opportunities in PgX.

Chapter 1:

The Changing Economics of Pharmacogenomics (PgX)

Despite growing evidence supporting its role in improving patient care and reducing costs, PgX suffered a setback in reimbursement when the Centers for Medicare & Medicaid Services (CMS) assigned coverage decisions to regional Medicare Administrative Contractors (MACs) in 2015, in effect rolling back coverage that was previously allowed. With the lack of a unified national policy, clinical labs are required to seek reimbursement from individual MACs and meet varied sets of criteria, such as clinical utility studies and supporting statements of medical necessity from physicians. Overall, the longer-term outlook on PgX reimbursement is still favorable as evidence of its value continues to accumulate and awareness among physicians increases. And the emergence of accountable care organizations is adding a new payer to the traditional mix of Medicare and private insurance.

"We are seeing a shift right now to value-based care. … There is definitely growth in that area because people managing risks for their patients recognize that improved medication management can really drive down the cost of care. In particular, one area of focus for us is improving polypharmacy management."

Kristine Ashcraft, CEO,
Genelex Corporation,
Seattle, Washington

Chapter 2:

The Critical Relationship Between Labs and Practitioners

Cardiology, psychiatry, pain management and oncology are the clinical specialties most likely to order PgX. Primary care physicians are joining in, as they increasingly prescribe many of the same medications, especially to elderly patients, many of whom suffer from chronic diseases and often take multiple medications.

"Physicians don't have time to research what a CYP2D6 poor metabolizer is, nor do they have time to read a 65-page report. … This means labs have to do the intellectual heavy lifting—the dry lab work—to make sure results are reported in a manner that is useful to physicians."

Bronwyn Ramey-Hartung, PhD, CEO, Phoenix Lab Consulting, Louisville, Kentucky

"The point of ordering these tests is to manage medications. Then it's a matter of at what point do you order it. A lot of physicians are doing that proactively rather than waiting until an initial prescription fails, and that is what we have to encourage through education. We also have to keep physicians updated about new genes that are added to our panels."

Tariq Adwan, PhD, Director of Research and Development, Alpha Genomix Laboratories, Lawrenceville, Georgia

Communication with physicians is a top priority. To help physicians maximize the value of PgX, labs must provide them with an easy-to-read, actionable report that summarizes patient results and how the results translate into clinical decisions. Just as important is setting realistic expectations and guiding physicians on which patients are most likely to benefit from PgX.

Investments in physician education and having medical science liaisons on staff to provide ongoing consultation to physicians are important, especially as PgX expands into other clinical specialties and as physicians are called upon to provide statements of medical necessity to support reimbursement. And as genome sequencing and companion diagnostics drive new PgX applications, labs will find that investing in physician education can lay the groundwork for a successful relationship.

Chapter 3:

Clinical Labs and PgX: Quality and Best Practices are The Goal

Inside medical laboratories, lab directors strive for quality results and efficiency—which means delivering high-quality PgX results to physician clients in a timely and cost-effective manner. Currently, an average turnaround time (TAT) of three to five days is satisfactory to physician clients and readily achievable by labs. However, reducing TAT is a factor as competition in PgX intensifies. And in some situations (e.g., when ordered by surgeons for perioperative pain management) a 24-hour TAT or better may be necessary.

"I think incorrect test results are certainly the biggest risk any clinical lab can have."

Weike Mo, PhD, FACB,
Technical Director,
Molecular Testing Labs,
Vancouver, Washington

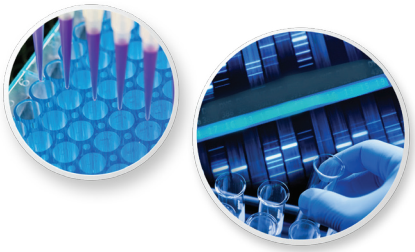
"One of the worst bottlenecks is repeat analysis, especially when faulty results are discovered after the fact. This can compromise credibility with physicians and is costly for labs that do not have the workflow or equipment in place for small-scale repeat analysis, such as a single SNP assay as opposed to an entire panel."

Bronwyn Ramey-Hartung, PhD, CEO,
Phoenix Lab Consulting,
Louisville, Kentucky

Quality is paramount from multiple perspectives—patient care, liability, professionalism and the cost of repeat analysis.

In the drive for accurate, error-free results, disciplined quality control, adherence to guidelines and maintaining accreditation are a given, as are good practices such as proper care of reagents and attention to expiration dates.

Chapter 4:



How Automation of DNA Extraction Reduces Error and Improves Efficiency

"Automation is good for reducing human error and getting more consistent results and in a shorter time. This is especially important in DNA extraction, the critical first step."

Weike Mo, PhD, FACB, Technical Director, Molecular Testing Labs, Vancouver, Washington

"Ultimately, the quality of DNA extraction is really the main determinant of how well testing is going to be done downstream. … It typically boils down to DNA quality."

Tariq Adwan, PhD, Director of Research and Development, Alpha Genomix Laboratories, Lawrenceville, Georgia

"As we look toward expanding our testing capabilities and wanting to be ready for an influx of samples, we look for ways to improve throughput. DNA extraction is one example where automation really makes sense."

Bradley A. Moss, President, Patients Choice Laboratories, Indianapolis, Indiana

Without exception, medical lab directors point to automation as the way to reduce human error and to ensure more consistent processes and results. Automation also improves throughput, boosts efficiency and helps expand capacity, especially important with the shortage of trained lab personnel.

Our expert panelists unanimously pointed to DNA extraction as perhaps the single most time-consuming and labor-intensive step and, from a quality perspective, the one that can benefit the most from automation. A high-quality DNA specimen will also reduce costly repeat testing.

A recent study comparing five automated DNA extraction platforms highlighted some workflow parameters to consider *Click here to access Study Summary.*[6] In addition to comparison studies like this, a thorough evaluation of available publications and studies can help guide selection of the platform most appropriate for specific lab requirements. Another important source of information, when selecting new extraction instrumentation, is the experience of other labs. For example, to see one pharmacogenomics lab's experience performing buccal swab extractions with the MagNA Pure 96 system from Roche, click here.[7]

Chapter 5:

Why Medical Necessity and Actionable Results are Key to Reimbursement

PgX today runs the gamut from FDA-approved, kit-based IVDs to laboratory-developed tests (LDTs). There are limited commercially available plug-and-play systems and minimal standardization. This puts the responsibility on medical labs to integrate instrumentation and reagent offerings from multiple vendors and to design, optimize and validate the workflow to meet quality and efficiency goals.

Proven technology platforms are cited by some medical lab directors as a way to reduce the unknown in ensuring quality results and, indirectly, regulatory concerns. Instrumentation that is IVD-labeled is strongly preferred, although other factors such as compatibility with current lab workflow are also important. FDA approval also plays an important role in companion diagnostics, where PgX is integral to approval of a therapy and regulatory clearance is a key consideration as early as the clinical trial phase.

"Some PgX labs start off using an RUO instrument for extraction, such as the MagMax, only to realize later that the instrument is not GMP-compliant or IVD-labeled, nor does it have the basic contamination control safeguards needed for routine clinical work."

Liz Thompson, COO,
Clinical Lab Consulting, LLC,
Portland, Oregon

"IVD-labeled devices can provide the best capabilities in sample tracking and audit trails."

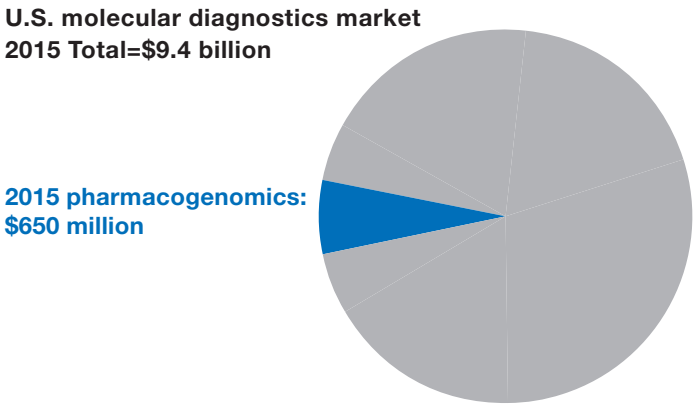
Bronwyn Ramey-Hartung, PhD, CEO,
Phoenix Lab Consulting,
Louisville, Kentucky

Reimbursement risk continues to be a challenge for clinical labs and pathology groups. Labs must, first and foremost, make sure that the tests they offer deliver actionable results and have demonstrated medical necessity. Published studies and guidelines are a starting point, but labs must be prepared to work with physicians to demonstrate clinical utility of the lab's offering.

Table 1: U.S. Molecular Diagnostics Market

Sector	2012 Estimate	2013 Estimate	2014 Estimate	2015 Estimate	CAGR 2012-2015
Pharmacogenomics	**0.43**	**0.49**	**0.56**	**0.65**	**15%**
TOTAL	**7.5**	**7.8**	**8.5**	**9.4**	**8%**

Market estimates are in billions (U.S. dollar)
CAGR=compound annual grow rate



Source: G2 Intelligence, *U.S. Molecular Diagnostic and Genomic Testing 2013 – 2015: Laboratory Industry Analysis, Trends, and Forecasts*, © 2013 Kennedy Information, LLC

Chapter 6:

Getting Started: The Elements of a PgX Practice for Pathologists and PhDs

Success in the PgX space requires a combination of good science (a clinically relevant test menu, reliable and actionable results), close communication with physicians, and good business, founded on a viable reimbursement strategy and a solid operating plan.

For labs that are just getting started, one effective approach to build the business may be to look for a fit with the existing client base. For example, toxicology labs may find that they can leverage the testing needs of existing clients who have a patient population that can benefit from PgX testing. In any case, all three components—the science and technology, operational infrastructure and reimbursement—must be part of an integrated business plan.

"Be sure you understand the reimbursement landscape. And have a team and a plan in place to prove the clinical utility of your offering.

Kristine Ashcraft, CEO,
Genelex Corporation,
Seattle, Washington

"Build a team out before you do anything. Get the scientists in place, get all the guidelines, make sure you're compliant and your science is right. That's first and foremost. And you can do that with the right people."

Bradley A. Moss, President,
Patients Choice Laboratories,
Indianapolis, Indiana

"Make smart decisions on technology and make sure the workflow is suited to expertise within the lab. For labs that can afford it, I advise upstream automation for DNA extraction."

Bronwyn Ramey-Hartung, PhD, CEO,
Phoenix Lab Consulting,
Louisville, Kentucky

Chapter 7:

Conclusion: What Lies Ahead for PgX

Ongoing discoveries and advancing technologies continue to create opportunities for expanding PgX services. Keeping abreast of scientific advances in a highly competitive field is a given. Lab directors speak of the need to continue to update existing panels by adding new genes or introducing new, clinically actionable tests. Many are excited about the promise of genome sequencing and anticipate adding DNA sequencing to their test menus.

Increasingly, labs are looking to scientific collaborations and participation in industry groups such as the Association of Molecular Pathology, American Association of Clinical Chemistry, American Society of Human Genetics and Clinical Pharmacogenetics Implementation Consortium as important sources of new ideas that can drive the PgX field and expand lab services.

> *"Ideally, the PGx profile is re-evaluated in the context of the entire drug regimen every time a medication decision is made. That way, whether a physician is prescribing at the office or a patient is purchasing over-the-counter, the safest drug and doses based on current evidence can be selected."*
>
> *Kristin Ashcraft, CEO, Genelex Corporation, Seattle, Washington*

Expertise beyond traditional lab medicine will also be critical to the future of PgX. For example, increasingly complex drug regimens demand more participation by the pharmacist in patient care. Another significant growth area is data analysis. In the short term, this means translating test data to actionable results for physicians. A growing opportunity on the horizon is the use of informatics to maximize a patient's PgX profile over the patient's lifetime and not just for the immediate need. Perhaps a pharmacogenomics profile for all patients is in the not-too-distant future.

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Appendices

A-1
About Roche Diagnostics

Roche is a global pioneer in pharmaceuticals and diagnostics focused on advancing science to improve people's lives. The world's largest biotech company, Roche offers truly differentiated medicines in oncology, immunology, infectious diseases, ophthalmology and diseases of the central nervous system. Roche is also the world leader in in vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management. The combined strengths of pharmaceuticals and diagnostics under one roof have made Roche the leader in personalized healthcare – a strategy that aims to fit the right treatment to each patient in the best way possible.

Roche Molecular Diagnostics offers a comprehensive portfolio of IVD and lab-developed test solutions with applications in women's health, virology, HAIs, blood screening, genomics and oncology. We are committed to working with our lab and clinician partners to deliver innovative solutions that help improve the management of disease, one patient at a time.

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2015 employed more than 91,700 people worldwide and invested CHF 9.3 billion in R&D. For more information, please visit www.roche.com or usdiagnostics.roche.com.

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About David Lahm

David Lahm is currently a marketing manager in the molecular automation group at Roche Diagnostics, which offers a comprehensive portfolio of IVD and lab-developed test solutions with applications in women's health, virology, HAIs, blood screening, genomics and oncology. With more than five years of experience in the research and clinical lab markets, he manages technology at the intersection of translational science and lab-developed diagnostic testing. Lahm holds an MBA from Purdue University.

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About DARK Daily

"Dark Daily is a concise e-news/management briefing on timely topics in clinical laboratory and anatomic pathology group management. It is a solution to the dilemma facing anyone in the laboratory profession.

DARK Daily is a concise e-news/management briefing on timely topics in clinical laboratory and anatomic pathology group management. It is a solution to the dilemma facing anyone in the laboratory profession. New developments, new technology, and changing healthcare trends make it imperative to stay informed to be successful. At the same time, the Internet, cell phones, blackberries, laptop computers and wireless devices are overwhelming any one individual's ability to absorb this crushing Tsunami of data.

DARK Daily is a quick-to-read, easy-to-understand alert on some key development in laboratory medicine and laboratory management. It has no counterpart in the lab world. Why? Because it is produced and written by the experts at THE DARK REPORT and The Dark Intelligence Group, who know your world, understand your needs and provide you with concise, processed intelligence on only those topics that are most important to you!

You will find DARK Daily to also be an exceptionally valuable resource in laboratory and pathology management. Some of the lab industry's keenest minds and most effective experts will be offering their knowledge, their insights and their recommendations on winning strategies and management methods. Many of these experts are unknown to most lab directors. As has proven true with THE DARK REPORT for more than a decade, DARK Daily will be your invaluable— and unmatched—resource, giving you access to the knowledge and experience of these accomplished lab industry professionals.

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About The Dark Intelligence Group, Inc. and THE DARK REPORT

"Membership is highly-prized by the lab industry's leaders and early adopters. It allows them to share innovations and new knowledge in a confidential, non-competitive manner.

The Dark Intelligence Group, Inc., is a unique intelligence service, dedicated to providing high-level business, management and market trend analysis to laboratory CEOs, COOs, CFOs, pathologists and senior-level lab industry executives. Membership is highly-prized by the lab industry's leaders and early adopters. It allows them to share innovations and new knowledge in a confidential, non-competitive manner. This gives them first access to new knowledge, along with the expertise they can tap to keep their laboratory or pathology organization at the razor's edge of top performance.

It offers qualified lab executives, pathologists and industry vendors a rich store of knowledge, expertise and resources that are unavailable elsewhere. Since its founding in 1996, The Dark Intelligence Group and THE DARK REPORT have played in instrumental roles in supporting the success of some of the nation's best-performing, most profitable laboratory organizations.

The Dark Intelligence Group (TDIG) is headquartered in Austin, Texas. This location makes it very accessible for any laboratory organization seeking input, insight and support in developing their business operations, creating effective business strategies and crafting effective sales and marketing programs that consistently generate new volumes of specimens and increasing new profits. The Dark Intelligence Group, Inc. owns and operates two Web sites in the TDIG Website network:

http://www.DarkReport.com

http://www.DarkDaily.com

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About the *Executive War College on Laboratory and Pathology Management*

Every spring since 1996, the lab industry's best and brightest gather at the *Executive War College on Laboratory and Pathology Management* to learn, to share and to network. Many consider it to be the premier source of innovation and excellence in laboratory and pathology management.

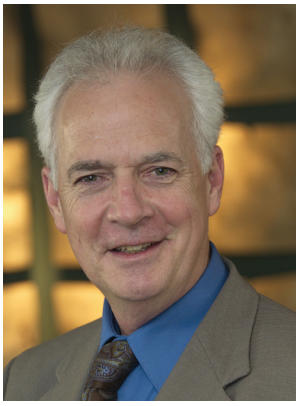
Each year, a carefully selected line-up of laboratory leaders and innovators tell the story of how their laboratories are solving problems, tackling the toughest challenges in lab medicine and seizing opportunities to improve clinical care and boost financial performance. The *Executive War College* is the place to get practical advice and solutions for the toughest lab management challenges. A unique case study format brings participants face-to-face with their most successful peers. They tell, first hand, how their laboratory solved intractable problems and successfully used new technology.

Many lab management secrets are shared, along with specific "what-not-to-do's" gained from hard-won experience! It's not pie-in-the-sky theory, but useful knowledge that can be put to use in any lab. The *Executive War College* offers superlative networking, with lab administrators and pathologists attending from countries as far away as the United Kingdom, Germany, Brazil and Australia. It makes the *Executive War College* a melting pot for all the best ideas, new lab technologies and management strategies now reshaping the laboratory industry. It's also become a recruiting ground used by headhunters and major lab organizations.

In the United Kingdom, The Dark Intelligence Group and the Association of Clinical Biochemists (ACB) have co-produced a meeting every February since 2003. Known at *Frontiers in Laboratory Medicine* (FiLM), it attracts laboratory leaders and innovators in the United Kingdom. Also featuring a case study format, this meeting pioneered the international laboratory side-by-side case study, where a North American laboratory and a United Kingdom laboratory prepare a comparison of best practices and an operational assessment of their two organizations.

In September 2005, a laboratory management meeting called *Executive Edge* was conducted in Toronto, Ontario, Canada, by The Dark Intelligence Group and QSE Consulting. It provided pathologists and lab directors in Canada with a customized meeting devoted to the strategic and operational issues of laboratory management in Canada.

A-6
About Joseph Burns



Joseph Burns is the managing editor of The Dark Report and a contributing editor for Dark Daily. An independent journalist in Falmouth, Mass., Burns has covered health care since 1991 and clinical laboratories since 2004. He writes for a variety of publications, including Managed Care magazine (where he is a contributing editor), Hospitals & Health Networks, and Healthcare Finance News. In addition, he is the insurance topic leader for the Association of Health Care Journalists and has worked as a writer and editor for The Commonwealth Fund, the Health Care Incentives Improvement Institute, the National Business Coalition on Health, the National Committee for Quality Assurance, and the National Quality Forum. Burns has edited books on health care business strategies for Faulkner & Gray and Panel Publishers and was editor-in-chief of Business & Health magazine, formerly published by Medical Economics Co., and later was a contributing editor and columnist for Managed Healthcare Executive magazine. He began his career as a journalist in Connecticut, working as a newspaper reporter for The Wallingford Post and the Meriden Record-Journal and as a copy editor, reporter, and regional news editor for The Hartford Courant, the nation's oldest newspaper. While working for The Courant, he taught news writing at the University of Connecticut.

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