WhitePaper

A Lab Leader's Guide To Pharmacogenomic Testing (PGx):

Cloud-Based Software Reporting of PGx for Hospitals, Health Systems and Clinical Laboratories

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Introduction:

An Overview of Pharmacogenomic Testing and Clinical Services

These genes (CYP450) code for the enzymes that are responsible for metabolism of more than 70 percent of prescription drugs.

Pharmacogenomics (PGx) is the study of how an individual's genetic makeup affects their response to drugs. During the course of a clinical trial to approve a drug, the proper dosage and various adverse events (negative side effects) for the drug's label are typically based on an average response in the trial's patient population.

In reality, there is a great deal of variability in how people respond to medications. It is estimated that 20 to 95 percent of patient variability to medications has a genetic basis.[1]

Pharmacogenomics (PGx) utilizes genomic markers to select the appropriate treatment for the patient in order to ensure drug efficacy while minimizing the risk of toxicity.

These biomarkers exist on genes that encode proteins which are involved in the pharmacokinetics (PK) or pharmacodynamics (PD) of the drug. PK is essentially what your body does to the drug in order to clear it from your system. PD is how the drug affects your body.

Several genes are responsible for differences in drug metabolism and response. The most common are the Cytochrome P450 (CYP) genes. These genes code for the enzymes that are responsible for the metabolism of more than 70 percent of prescription drugs.[2]

Variations in the CYP genes inf luence how quickly or how thoroughly individuals metabolize specific drugs. Based upon well studied genetic variations pharmacogenomic testing classifies individuals as poor, intermediate, normal, or ultra-rapid metabolizers for specific drugs. "Greater than 75% of patients have genetic variations that categorize them outside of 'normal metabolizers'."[3]

"Knowing about patients' genetic variations can help physicians avoid drugs that may cause adverse reactions."

A "poor" metabolizer often means the drug is eliminated slowly and may accumulate. These patients may require a lower dose to avoid the toxic accumulation. For some drugs, called prodrugs, the body's metabolism converts the drug into its active form. A poor metabolizer of a prodrug may experience decreased efficacy and might require an alternative medication.

On the other end of the spectrum, an "ultra-rapid" metabolizer may mean the drug does not work well enough because the drug is metabolized very quickly, and requires a higher dose to offset that fast metabolism. In the case of prodrugs, it may mean increased efficacy, with a rapid onset of the drug's effect, requiring a lower dose to prevent toxic accumulation.

Understanding an individual's pharmacogenomics is two-fold: it requires an understanding of how the patient's genetic profile affects their response to specific types of drugs, and it requires an understanding of the specific drugs' pharmacological profiles.

Some of these effects can be life threatening. "Knowing about patients' genetic variations can help physicians avoid drugs that may cause adverse reactions."[4]

Another term often used in connection with pharmacogenomics is "personalized" or "precision medicine." Given that every individual has a unique response to various medications, the concept of precision

medicine is that patients will routinely have PGx tests performed so that their physicians can tailor their treatments to thier individual genomic profile. PGx is only one aspect of precision medicine, but it is one of the first to gain wide adoption and will likely be the first to be recognized as the standard of care.

PGx testing provides a very complex mix of raw data. The key is to interpret it and give it meaning.

In 2010 the FDA issued a black-box warning for CYP2C19-linked poor metabolism for anti-platelet drug Plavix.[5] The warning alerted doctors and patients that patients with diminished CYP2C19 function were poor metabolizers of Plavix and would be less protected against a secondary event after acute coronary syndrome or percutaneous coronary intervention than normal metabolizers of the drug. The FDA has since placed PGx information on over 190 medications.[6]

Although it is clear that PGx testing is valuable, it presents a number of challenges to physicians, clinical diagnostic laboratories and healthcare institutions. A primary challenge is in analyzing the data from PGx tests in context with patient's medication lists in order to provide actionable intelligence that a busy physician can use to drive good medical care, in a cost- effective, efficient and reliable manner.

PGx testing yields a complex mix of raw data and the key is to interpret it and give it meaning. Effective application of this data in the clinic requires recognition of five key points:

- The clinical evidence for PGx requires expert curation
- There are numerous gaps in the data, such as unstudied genotypes
- There is a wide range of evidence quality produced by clinical studies
- Real genomic data is "messy," i.e. it is complicated and not all genotypes are straightforward
- Genetic data is limited without a patient's clinical context

This paper will discuss the importance of PGx testing in today's healthcare environment, the obstacles physicians, laboratories and hospitals face when launching an evidence based pharmacogenomics program, how it can be used to drive patient care, and the role cloud-based software can play in making PGx testing a practical and cost-effective solution.

Chapter 1:

PGx, Healthcare Reform and Improving Patient Outcomes

Pharmacogenomics has the potential to have significant impact on the third goal, reduction of costs, and on the overall quality goals.

The Patient Protection and Affordable Care Act (PPACA, better known as ACA) was signed into law on March 23, 2010. It had three primary goals: expand access to health insurance, protect patients against arbitrary actions by insurance companies, and to maximize value by improving the quality of healthcare.

Pharmacogenomics has the potential to have significant impact on the third goal of reduction in costs, and improving on the overall quality of care.

In addition to those overarching goals, the ACA established the Patient-Centered Outcomes Research Institute (PCORI). The PCORI is a private, nonprofit institute whose goal is to identify national health priorities and to provide for research to compare the effectiveness of health treatments and strategies.

"Overseen by a board of governors with broad stakeholder involvement and assisted by expert advisory panels, its methodology is to develop a standard set of methods to require researchers to take into account subpopulations, genetic and molecular subtypes, and the phase in the innovation cycle of the treatment modality."[7]

The American Medical Association[8] cites six ways in which pharmacogenomics can lead to an overall decrease in healthcare costs.

1. Decrease the number of adverse drug reactions.
2. Decrease the number of failed clinical drug trials.
3. Decrease the amount of time it takes for a drug to be approved.
4. Decrease the length of time patients are on medication.
5. Decrease and potentially eliminate the trial-and-error approach to find an effective therapy for patients.
6. Decrease the effects of the disease on the body through early detection.

According to a 2012 RNCOS Industry Research Solutions report, genomic testing is among the fastest growing parts of the lab market, representing revenue of $1.5 billion worldwide.

From the perspective of the physician, pharmacogenomic testing has at least three benefits for patients.

- PGx saves patients money on ineffective medications.
- Testing prevents patients from having avoidable unpleasant or possibly fatal side effects related to some medications.
- Precision prescribing improves the efficacy of the physician's comprehensive treatment plans, which leads to improved quality of life.
- Testing also has the potential to reduce visits to the doctor's office and alleviate shortages in healthcare personnel and facilities.

In addition, the Center for Disease Control and Prevention estimates that the overall 1 million emergency room visits and 280,000 hospitalizations for Adverse Drug Events (ADEs) cost the United States about $3.5 billion annually. It is estimated that as much as

40% of these events are preventable. Reducing this figure can have a significant impact on healthcare expenses in the U.S.[9]

Insurers have been slow to adopt reimbursement strategies for pharmacogenomic testing, but evidence continues to build supporting testing.

"Physician use of select PGx tests appears to be gradually increasing."

A Reportlinker 2017 report shows CAGR at 10.4% and global revenue at $10.3 billion by 2025. Concert Genetics is also reporting that there are 10 new genetic tests added in the US market daily.

In 2013 Michael D. Graf et al.[10] published a study in Personalized Medicine that looked at 206 insurers to determine their policies regarding genetic testing, pharmacogenomic testing included. They found that about a third of insurers had at least one genetic testing policy, although consistency between payers was only moderate. The areas in which genetic testing was most commonly addressed were in oncology and the pharmacogenetics aspects of personalized medicine. About half of the policies excluded a particular genetic service, and, unfortunately, about half of the insurers had at least one out-of-date policy.

The study concludes: "With the continued growth of personalized medicine and the introduction of complex genetic tests into the market, payers will need to increase the coverage policies devoted to these areas of clinical care. Advances in testing technology, including whole- genome sequencing, as well as changes in healthcare policy being implemented to reduce costs, such as those addressed by the Affordable Care Act, will continue to challenge payers. High-quality evidence reviews and governmental and professional organization guidelines will help build consistency of payer coverage. Payers must be prepared to dedicate resources and partner with genomic experts to ensure that their coverage policies are current and consistent with standards of care. Failure of coverage policy to keep pace with

innovation may limit the availability and impact of personalized medicine tests in medicine."

Although current reimbursement is variable, there is some good news. Andrew Hresko and Susanne B. Haga published a 2012 article in the Journal of Personalized Medicine titled "Insurance Coverage Policies for Personalized Medicine." They concluded, "Improving physician and patient awareness of tests will be essential for adoption. Little data exists about patient consent of personalized medicine tests, but public interest has been reported to be high. Physician use of select PGx tests appears to be gradually increasing."

Chapter 2:

Obstacles to Overcome When Launching a PGx Program

Once clinicians find value in PGx testing for driving patient care, it will generate more data, which will further support the need for testing and reimbursement.

There are three significant components needed to determine the value of a pharmacogenomic test. They are:

1. **Analytic Validity.** How accurate is the test in sensitivity and specificity? Does it accurately identify a particular genetic variant?
2. **Clinical Validity.** Are the genetic variants being tested correlated with a specific disease or condition, i.e. phenotype, and that do they accurately predict increased risk for abnormal response to a drug.
3. **Clinical Utility.** Are the test results actionable and will they drive healthcare decision making and improve outcomes. In many ways, Clinical Utility is the key to both physician engagement and payer reimbursement policies. Once clinicians find value in PGx testing for driving patient care, it will generate more data, which will further support the need for testing and reimbursement.

It's fairly clear that payers will not pay for a pharmacogenomic test that does not have analytic and clinical validity and clinical utility. (Consumers, on the other hand, might, if they believe it has value to them). While outside the parameters of this report, Dr. Matt McCarty, owner and director of Genotox Laboratories in Austin, Texas, notes that, "Interest on the consumer end is markedly different. Consumers understand there are other factors involved and are very interested in how unique they are individually. They want to figure out why they

can take a medication and have specific side effects, but, for instance, their children may not have those side effects."

Although coverage is inconsistent today, PGx test reimbursement can be lucrative according to Dr. Tootie Tatum, PhD, HCLD, a clinical lab consultant. She notes certain tests can be very profitable for the lab, particularly in comparison to toxicology and other commodity tests.

Although coverage is inconsistent today, PGx test reimbursement can be lucrative.

As mentioned earlier, not all PGx tests are reimbursed or are reimbursed inconsistently. However, as more and more evidence emerges on the clinical utility and clinical validity—in other words, as it drives treatment and has the data to back it up—insurers will be more likely to reimburse.

Barriers to Entry

From the laboratory or hospital perspective, there are several barriers that have to be overcome. First, capital equipment costs are fairly high, with specialized instrumentation only available from a handful of vendors. Tests and reagents need to be validated as well, which requires that laboratory technologists and laboratory directors have a good understanding of the science involved. There are also regulatory hurdles with CLIA inspections and CAP accreditation.

And most relevant to this report, there is a need for a system that can help interpret PGx tests.

The genes typically tested in PGx testing are CYP genes. There are about 60 CYP genes in humans and the enzymes they code for are usually found in liver cells, although many are found throughout the body. About ten of those genes play the largest role to metabolize external substances like medications and pollutants and are responsible for 70 to 80 percent of drug metabolism.

The number of polymorphisms in these 10 genes that correlate to hundreds, possibly thousands of drug responses, becomes very complex to interpret. A skilled PhD or MD with training in the area can do it, but it will be time-consuming. Tatum says, "At the end of the day you have this highly complex multi-function test. Some have 45 to 63 SNPs [single-nucleotide polymorphisms] they're typing and within the complex, the genes, duplications and deletions, etc., there's variation… So it's a lot of data and if you're not using an FDA-cleared system it's sort of a train wreck to try and report."

A system or service that provides analysis and is in the business of staying on top of current research and validation is highly recommended.

A system or service that provides analysis and is in the business of staying on top of current research and validation is highly recommended. Most laboratories will find that performing the analysis themselves become ineffective from a cost perspective because it is extremely time-consuming.

On a broader scale, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has developed practical guidelines for genetic laboratory test results as they apply to specific drugs. They keep an active database of clinical recommendations and dosing information for various specific medications.

Chapter 3:

Using PGx to Enhance Clinical Utility and Patient Outcomes

Translational Software® operates as a cloud-based Software-as-a-Service solution.

Genotox Laboratories operates in Austin, Texas. The laboratory focuses on two modalities: genetic testing for a patient's ability to metabolize certain drugs, and as a comprehensive urine drug screen laboratory. It operates out of a 3,300-square-feet facility and performs a little over 5,000 samples monthly. Of those 5,000 samples, about 150 to 200 are pharmacogenomic tests. The laboratory provides services all over Texas, Florida, Tennessee, Indiana and other states.

Dr. Matthew McCarty, who owns and operates the laboratory, says, "We're currently running a panel of 15 pharmacogenomic tests. We utilize Translational Software® and the company provides us evidence-based translation for our customers, to provide the actual results."

Translational Software® operates as a cloud-based Software-as-a-Service solution. For small laboratories, the company's PGx Portal is available via the Internet, which allows laboratories to upload genetic test results and patient demographics through a Web interface. It also has a reporting platform that the lab can use to produce reports directly for delivery to customers.

Larger labs with laboratory information systems (LIS) can connect through an HL7 interface to the portal. In this mode, the LIS provides the translational service with patient demographics and the service puts out PDF reports encapsulated in HL7 messages.

Because the system is cloud-based, it is highly scalable and delivering it in a Software-as-a-Service (SaaS) business model lowers the total cost of ownership. Given the current state of healthcare economics, laboratories find it much less expensive to outsource this service than to build one-off systems. And these cost savings help to ensure that PGx testing decreases overall healthcare costs.

"Translational® comes up with an actionable report for a physician to quickly look at a patient's medication."

McCarty says, "I think it's a very reasonable cost, but what will ultimately drive these sorts of tests' success will be third-party payers willing to pay for the tests, or get out of the way and allow sales of genetic testing by pharmacists on a cash-pay basis."

McCarty says, "Translational® comes up with an actionable report for a physician to quickly look at a patient's medications. It looks at what the patient is currently on that is causing issues. Then on the second page of the report, it gives an option of medications that could be better metabolized, so better tolerated. The actual report, I think, ref lects more accurately information a physician can use."

Kyle Fetter, Vice President of Advanced Diagnostics for XIFIN, points out that Translational® has several key advantages. One is that because they are accumulating huge amounts of PGx data over time, "their analysis is getting better and better and better. They're getting that because they're getting so many different patient samples that you wouldn't get if you were just one lab."

A second thing, Fetter says, "I think a solution like Translational® will challenge the economics of any lab, at least in the diagnostic space. In the PGx space where you have genes that have already been validated and there is already research out there, I think Translational® will probably permanently change the economics of developing those reports on your own."

It should be emphasized that PGx interpretation is complex. It's not simply a matter of looking up a gene mutation and saying, "As a result of mutation Y the patient will metabolize drug X more quickly than a typical patient." Some drugs, like Simvastatin, are affected by a single SNP. Other drugs like Codeine are affected by multiple haplotypes and copies of a gene. Drugs like Warfarin are affected by specific combinations of genes that are different between Caucasians and non-Caucasian patients.

There are definite advantages to a service that specializes in PGx interpretation.

There are definite advantages to a service that specializes in PGx interpretation. They have the expertise to stay updated on the latest findings and drug-gene associations.

Chapter 4:

Understanding the Role of Cloud-Based Software for PGx Reporting

A laboratory report must integrate PGx data efficiently so it can be utilized in a busy medical practice.

As mentioned above, PGx testing is complex, involving the interactions of 60 to 200 variations of approximately 15 genes that have actionable data for 150 drugs. Even larger numbers are still being researched, but have yet to provide enough data to be clinically useful. It is a daunting challenge for laboratory directors to stay current on the genetic data pouring in to reliably and consistently interpret PGx test results.

Further complicating the interpretation of the data is that the typical physician isn't interested in a 25-plus page report detailing every SNP identified and how the patient responds to hundreds of different types of drugs. There is undoubtedly a role for that sort of information in the electronic medical record, but what the physician wants is quickly accessible, actionable information that can drive healthcare decision making.

Therefore, a laboratory report must integrate PGx data efficiently so it can be utilized in a busy medical practice.

Another way to put it is that the laboratory either needs to develop a good, efficient and elegant way of interpreting PGx test results and reporting it, or the laboratory must utilize a service that does.

Translational Software®

At the moment, most instrument vendors provide labs the ability to validate and report the genotypes for test results. Some also can "call" the appropriate diplotypes and even clinical phenotypes for the result. What is more difficult is to incorporate into the lab's workflow is the ability to analyze these results and provide actionable guidance for the end user that is presented in a way that is easier to digest.

"So even manufacturers will recommend a group like Translational Software® because that's what Translational® does. Translational® makes complex information into easily readable human reports."

Kyle Fetter says, "Traditionally the only competition for things like this has been manufacturers and they openly say they don't spend many resources on this, nor do they understand how these reports work. And they don't regularly work with ordering physicians. So even manufacturers will recommend a group like Translational Software® because that's what Translational® does. Translational® makes complex information into easily readable human reports."

Other companies may provide at least some PGx interpretation, or use PGx data as part of other services they may provide, but Translational Software® focuses specifically on the interpretation of PGx testing.

Tatum says, "Basically Translational® takes all of the genotypes and haplotypes and associated phenotypes. That's the first step and you can usually get that data fairly easily yourself. But the really nice thing is Translational® provides great drug dosing guidance and drug interaction guidance. I can't do that. There's just no way I have the time, plus that's beyond my scope of practice."

Translational Software® provides guidelines developed by the CPIC, of which they are members, the Dutch Pharmacogenetics Working Group (DPWG), the FDA and many other sources and makes these guidelines available to molecular diagnostic laboratories. Because Translational® is not a laboratory, they can focus on the evidence based informatics necessary to all laboratories and attract the

software and scientific talent necessary to produce a world-class solution.

With this information in their knowledge base, they take an evidence-first approach in working with labs. Given the knowledge of what specialties the lab is focusing on, they can determine what drugs are relevant, what genes affect those drugs, and which SNPs should be tested for the highest impact at least cost. With all this in mind, reports can be designed that target the pain clinic, psychiatrist, or cardiologist (among others) that the lab wants to reach.

What the end user receives is a report that focuses on the drugs or risk factors that are highly relevant to the medications that the patient is taking and the clinical decisions faced by the physician.

What the end user receives is a report that focuses on the drugs or risk factors that are highly relevant to the medications that the patient is taking and the clinical decisions faced by the physician. The result may be as small as two pages, or upwards of 36 pages when it includes a broad selection of genes and medications and monographs. Tatum says, "But the bread and butter is the first page or two. Most clients I work with, the key results are on the front. There it essentially says, 'For this patient, these are the drugs you told us they were on. Here is some guidance for working with this patient.' And they color code it as green, yellow and red, with lists of other drugs that should be of concern."

McCarty points out that he has the background to build a similar database himself. "It's just work and going into the actual research field and making the results more palatable. We considered doing it at one point, but it's quite an undertaking, pulling in the research data and putting it into a format that's usable for physicians in their practices."

Tatum adds that at least one of the prominent PGx systems does provide a report, but it's not formatted. "It's super ugly, so there are mechanics you have to go through to make it usable. It's also not

comprehensive. You can't really use it for all the tests. They will give you some information, but not the interpretation. It becomes really complicated."

She also points out that the laboratories she advised initially were resistant to paying additional money per test to utilize Translational's® service. "We tried to use the instrumentation's report, but it wasn't efficient to use. Eight months later management said, 'Maybe we need to go with Translational®,' and I said, "'Yes, that's right.'"

"Translational® is probably as close to an out-of-the-box software solution as you can get and it's always getting better."

In addition to content issues are operational considerations that are important to delivering a cost effective service. By supporting all major testing platforms, laboratories can choose the technology that is the most reliable and cost-effective choice for their tests. Specialized reporting for allele frequencies enables labs to spot inconsistencies quickly and a deep understanding of the results allows Translational® to help labs avoid re-runs.

"The beauty of Translational®," Fetter says, "is if you have your laboratory information system (LIS) and your billing system, you plug into Translational's® service. You make sure you can get your instrumentation connected to them, and they take your raw data and generate these reports. I think it's very compelling for any laboratory that has both an LIS and all of those other pieces."

Fetter says that it's a little rare for XIFIN to need to recommend Translational® or any similar service. "Because we're more on the revenue cycle side, we try to stay out of giving people too much clinical advice. But we will say Translational® is probably as close to an out-of-the-box software solution as you can get and it's always getting better. And when it comes to PGx, I'm not sure we know of anyone else to recommend. Besides, Translational® has already

been chosen. It seems to me that it's usually the instrumentation manufacturer that suggested Translational®."

Advantages to a Cloud-Based PGx Service

There are numerous advantages to outsourcing PGx interpretation.

There are numerous advantages to outsourcing PGx interpretation. They include:

1. Lower costs by amortizing over many laboratories.
2. Faster time to market than home-grown solutions.
3. Faster turnaround time than manual report assembly.
4. More consistent end results than home-grown solutions.
5. Lower investment risk.
6. An evidence based proprietary knowledge base built on the most up-to-date PGx data available that is updated on a regular basis.
7. Report output is customizable to the laboratory's and ordering physician's specifications.
8. Reports adhere to your laboratory's brand standards.
9. At the moment, the service cost is 60 to 70 percent less than interpretation by a pharmacist.
10. Requires little to no IT support because it is SaaS-based.

Conclusion:

The Future

As more physicians utilize PGx testing and translational services, more clinical data is generated.

It has only been eight years since the FDA first put a black-box warning on a medication suggesting PGx testing, and in the interim somewhere between 120 and 130 drugs have been added that include explicit information about patient genetics. As more and more pharmacogenomic data is acquired and clinical usefulness validated, PGx testing is likely to be commonplace.

Numerous studies have been performed on various oncology tests, including PML/RARα for Arsenic trioxide (a mandatory FDA test recommendation), EGFR for Cetuximab (FDA recommended) and DPD for 5-fluorouracil (mandatory), and others supporting their clinical use.[12] The following table references four studies in which PGx testing showed significant clinical validity in the psychiatric setting.

Numerous additional studies are pending or already available supporting the clinical usefulness of PGx testing. In addition, as more physicians utilize PGx testing and translational services, more clinical data is generated.

Effectiveness of PGx testing in Psychiatric settings

Study	Important Findings	Utility
2011, Mayo Clinic – 200 outpatients PMID=23047243	44.8% reduction in depressive symptoms with initial PGx testing compared to 26.4%.	Improve Efficacy
2012, University of Illinois Department of Psychiatry – 96 over 1 year PMID=23511609	poor metabolizers of CYP2D6 or CYP2C19 had 69% more total healthcare visits, > 3-fold more medical absence days, 4-fold more disability claims	Improve Safety Reduce cost
2000, Eastern tate Hospital in Lexington- 100 inpatients PMID=10770465	Average cost to treat patients with extremes phenotypes for CYP2D6 (rapid and poor metabolizers) $4,00 to $6,000 greater than normal or intermediate metabolizers	Reduce Cost
2013, Danish Healthcare System, - 200 patients (RCT) PMID=23731498	PGx testing reduced costs among extreme metabolizers of CYP2D6 and CYP2C19 by 28%.	Reduce Cost

Over time the vision for PGx is that a genetic test will be performed early in a patient's lifetime and the results stored in their medical record.

Dr. McCarty, also opened a pharmacy where PGx tests are offered. "It takes the PGx information and uses it in medication therapy management (MTM) consultations, which are driven by the pharmacy benefit managers, who don't generally use PGx in their consultants." At least one of the goals is to decrease the amount of hit-and-miss prescriptions that either cause patients too many side effects, affecting compliance, or to more closely regulate dosage. One advantage to this approach is it doesn't necessarily have to be reimbursed, but can be implemented on a cash basis for interested consumers.

But in order for it to work, the data created needs to be manageable, updated and interpreted. It also needs to be boiled down and reported in a straightforward manner that drives patient care. The data needs to be constantly updated to keep up with current information about the drugs and implicated gene sequences.

Over time the vision for PGx is that a genetic test will be performed early in a patient's lifetime and the results stored in their medical record. From that point on, every medication decision can be guided

by the most current information about relationships between their unique genetic makeup and most safe and effective alternatives.

This report has provided an overview of pharmacogenomic testing and discussed how PGx fits into current healthcare goals. It discussed the obstacles healthcare providers, institutions and clinical diagnostic laboratories face in entering the pharmacogenomic testing market, including clinical validation, reimbursement, economics and reportability. And finally, it presented examples of how a cloud-based Software-as-a-Service platform such as Translational Software® can help healthcare providers hurdle those obstacles, leading to more precise healthcare diagnoses that can drive personalized medicine and improved healthcare.

A cloud-based Software-as-a-Service platform such as Translational Software® can help healthcare providers hurdle those obstacles, leading to more precise healthcare diagnoses that can drive personalized medicine and improved healthcare.

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Appendices

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About Translational Software®

Translational Software is at the forefront of integrating genetic information into mainstream clinical care.

Translational Software currently works with more than 70 molecular testing labs—serving over 20,000 practitioners—by providing market-focused services with end-to-end solutions to support physicians adopting Precision medicine.

Genomics-based testing focuses on a patient's ability to metabolize drugs through the liver's isoenzymes, and for many common prescriptions, a simple genetic test can provide significant insight into the likely efficacy or toxicity of a drug.

The company's powerful PGx Portal is an advanced, cloud-based solution that harnesses the company's proprietary knowledge base—developed from only the most current and relevant clinical evidence—coupled with advanced laboratory molecular data.

The Portal generates relevant reports for referring clinicians with easy-to-understand recommendations and guidance on therapeutic options for their medication management.

The goal: enhance the health care professional's diagnostic confidence, satisfaction and efficiency leading to better outcomes for the patient.

By transforming molecular data into information clinicians can easily interpret and understand, over 100,000 patients (and growing) now have new insights into the medications that are most appropriate for them.

As the founder of Microsoft's Biolt Alliance in 2005, Translational Software founder and CEO Don Rule recognized that while there were

brilliant scientists working on genomic technologies, they would require technologists to make it relevant in the clinical environment.

Founded in 2009, Translational Software was one of the first—if not the first—to understand the need for an interpretation industry separate from either the lab or equipment industries.

"Genetic data is a powerful tool when it is coupled with easy to understand interpretation and analysis," said Rule. "We integrate genetic test results into the clinical workflow, enabling doctors to understand the implications of test results."

The Translational Softwares' reports include information targeted to clinical specialties, and Portal can be integrated with existing Laboratory Information Systems (LIS) to significantly reduce costs and turnaround time.

The company's strength lies in its core competencies.

In this rapidly evolving marketplace, Translational Software enables healthcare providers to realize the promise of precision medicine. We simplify complex genetic data into evidence-based actionable recommendations to deliver genomic decision support in platform agnostic formats. Through the company's PGx Portal, knowledge base and Fast Healthcare Interoperability Resource (FHIR)-based API we complement the proficiencies of laboratories. Translational is currently expanding it reporting and interpretation to Wellness and Carrier screening as well as expanding pharmacogenomics to Pediatrics.

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About Mark Terry

Mark Terry is a freelance writer and editor specializing in clinical diagnostics, telemedicine, and biotechnology. He worked for 18 years in clinical genetics prior to turning to writing, and has published over 1000 magazine and trade journal articles, 20 books, and dozens of white papers and book-length market research reports related to the clinical lab industry. He is a member of the Association of Health Care Journalists and the Association of Genetic Technologists. For more information, visit his website at www.markterrywriter.com.

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About DARK Daily

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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:

THE DARK REPORT

http://www.DarkReport.com

DARK Daily
Clinical Laboratory and Pathology News/Trends

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.

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About Don Rule, Founder and CEO, Translational Software

As a leader at the intersection of life science and computer science, Translational Software CEO Don Rule is rapidly paving the way for genetic information to be a routine part of clinical care and improving patient outcomes.

Prior to founding Translational Software, Rule was the founder of Microsoft's BioIT initiative in 2005. He immediately understood that genetic data has powerful implications for clinical care but is too complex for the average clinician to interpret.

An accomplished software professional with a focus on life science—and experience in both IT and commercial software development—Rule has created a series of market-focused services delivering end-to-end solutions to support physicians adopting personalized medicine.

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About Houda Hachad, Pharm. D, M. Res.; Chief Science Officer, Translational Software

Dr Houda Hachad received her Pharmacy Doctorate and her Master of Research in Drug Metabolism & Clinical Pharmacology from the Henri Poincaré University in Nancy, France. When in France, she was involved in a research program at the Centre du Médicament, School of Pharmacy (1993-1998) and worked as a consultant for the World Health Organization on the NOMA bibliographic database.

Dr Hachad joined the University of Washington, School of Pharmacy for 10 years, and co-developed two knowledge-based technologies managed by the University's Center for Commercialization. She was involved in creating a revenue-based model for a drug interaction database (DIDB Platform; www.druginteractioninfo.org) used by the world's largest pharmaceutical firms, academic and government institutions. As the primary project designer of a pharmacogenetic database e-PKGene, she planned the IT development to meet the program's goals and objectives, and managed the project through Product launch. Dr Hachad has authored numerous peer-reviewed articles, book chapters and evidence-based guidelines in the field of metabolism & transporter-based drug-drug interactions.

In 2011, Dr Hachad joined Translational Software, a Seattle-based start-up company aimed at accelerating the adoption of personalized medicine by clinicians. As the Chief Science Officer, she is responsible for establishing the scientific strategy for the company and creating a pharmacogenetic knowledge base for decision support. She has recently joined the Clinical Pharmacogenetics Implementation Consortium (CPIC; www.pharmgkb.org/page/cpic) and is participating in developing evidence- based guidelines to facilitate the adoption of pharmacogenetics by clinicians.

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About Rick Shigaki, Vice-President Sales & Marketing, Translational Software

Anticipating upcoming reforms related to the pharmaceutical and clinical laboratory industries, Rick Shigaki is shaping the marketing strategies for Translational Software's proprietary pharmacogenetic SaaS platform, including distinguishing the clinical value of pharmacogenetic data.

For the past 20 years Shigaki has held business development and sales management positions in the healthcare business environment. His experience ranges from large multinational corporations, including 16 years at Pfizer, to leading-edge startup companies. Shigaki is a graduate of the University of Washington School of Business.

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