



Pharmacogenetics:

A Discussion with Industry
Experts about the State of
Affairs and Clinical Application

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At the recent Association for Molecular Pathology (AMP) 2014 annual meeting in Washington DC, Luminex hosted a panel discussion on the current state of pharmacogenetics (PGx) affairs, including laboratory adoption and the reimbursement landscape.

For those who were unable to attend this session, we have collected panel questions and the panelists' responses in the following comprehensive report format.

In this e-book, you'll learn:

- How laboratories view pharmacogenetic testing as a means to differentiate themselves
- The added value laboratories can provide to physicians and patients by offering pharmacogenetic testing
- Successful strategies used to improve reimbursement

We hope you find this informative. Please submit any questions to shenderson@luminexcorp.com.

The Panelists



Scott W. Blevins, RPh, MBA; *President and COO, GENETWORx:*

Mr. Blevins has over 20 years of experience in the health-care industry, with an emphasis in providing consultative services to physicians, including clinical and physician practice management advice. Prior to becoming a health-care business consultant, Mr. Blevins worked in various segments of the pharmacy industry, which included chain, independent, long-term care facility dispensing and consulting, and Pharmacy Benefit Management (PBM). Mr. Blevins also has a working knowledge of Healthcare Information Technology, Revenue Cycle Management, and Laboratory Services through his ownership interest in "Docs Billing Solutions." Mr. Blevins is a co-founder of GENETWORx. Mr. Blevins received his Bachelors of Science degree in Pharmacy from the Medical College of Virginia (M.C.V.) School of Pharmacy, and his Master's in Business Administration degree from the E. Claiborne Robins School of Business at the University of Richmond.



Sarah Jacobs-Helber, PhD, HCLD (ABB); *Laboratory Director, GENETWORx:*

Dr. Jacobs-Helber has over 20 years of clinical and laboratory experience in the field of genetics. She has authored a large number of peer-reviewed papers in the course of her research into the biology and genetics of cancer at both the National Institutes of Health and Virginia Commonwealth University. She has been in the clinical genetic testing area since 2006. She holds board-certification as a High-Complexity Clinical Laboratory Director (HCLD) from the American Board of Bioanalysts and is certified in molecular genetic testing by the State of New York.



Joan Kegerize, MS, JD, CPC; *Principal Consultant,*
GMBI Consulting:

Ms. Kegerize specializes in reimbursement and coding strategies, with emphasis in genetic services and diagnostic laboratory molecular pathology procedures. She has extensive experience in molecular diagnostic testing and reimbursement and works closely with manufacturers, laboratories, and industry to direct and implement reimbursement strategies for Medicare, Medicaid, and commercial payers. Ms. Kegerize received her genetic counseling training at the University of Pittsburgh Genetic Counseling Program. She earned her Juris Doctor degree from New York Law School and is admitted to the Bar in the state of New Jersey. Ms. Kegerize obtained certification as a Certified Professional Coder by the American Academy of Professional Coders.

1. Why do laboratories decide to offer pharmacogenetic testing and services in the first place?

JK Joan Kegerize: Laboratories are beginning to realize the importance of pharmacogenetics—which could be because of a laboratory scientist’s interest in molecular testing, or referring doctors requesting it. In the past, pharmacogenetic testing has been limited to cytochrome P450 testing for the cardiology core referrals. Now, we’re seeing an expansion of referring doctors and clinicians in psychiatric, psychotropic, and pain management fields who understand the benefit for their patient population.

SB Scott W. Blevins: When we were starting GENETWORx, there were two aspects to it that were very appealing. One, I felt this technology was available but providers were not benefiting from it.

Secondly, molecular diagnostics presently makes up about one-third of all the laboratory revenue. Pharmacogenetics is expected to grow at a 14.5% compounded annual growth rate through 2017.

This gave us an opportunity to create a business and fill a need, while at the same time, putting patient first. We feel we’ve been able to do that and really have some rewarding aspects as we think about the providers and the patients.

SJH Sarah Jacobs-Helber: Pharmacogenetic panel testing has become a powerful way to do our testing—we can use a more comprehensive approach to the testing, to allow the pharmacists who work with us to make overall recommendations. Not just for cardiology, pain, or psychiatric, but to address all of the patients’ different needs. The panel approach also allows us to process more samples more efficiently and more accurately. And it has fit very well into a workflow of other molecular genetic testing that we provide.

So in that respect, we brought it on because it worked very well not only from the pharmacy and the business standpoint, but also in a workflow environment for a clinical genetic testing laboratory.

2. What does GENETWORx do to increase utilization of pharmacogenetic testing by physicians and providers?

SB : One of the needs that we identified early on was genomics wasn't being taught to any extent. So, to present a typical test result to a clinician who may not know what an allele is makes it very difficult to empower them to utilize that to the benefit of themselves and/or their patient and treatment regimen.

We spent a lot of time and effort creating educational materials, and even had accredited continuing education for providers. Beyond that, we created a panel of Cytochrome P450s, which cover about 90% of the drugs that are metabolized today. And we don't just report the test result—we have our pharmacist look at the patient's whole medication profile in tandem with the test results to give what I'd call—more or less—a medication therapy management review, performed by the pharmacist. We're then able to provide that to the physician with those lab results, which are very important.

We're attempting to get away from shotgun therapy and optimize the drug regimen, which we believe will curb the cost of healthcare, particularly relating to adverse drug events, which cause 700,000 ER visits a year. We can save the healthcare system a lot more, and put the patient on the right drug the first time.

Additionally, an outcome of one of the recent studies suggests that we're no longer just looking at this from a drug-to-drug interaction standpoint, but from a drug-to-gene and drug-to-drug-to-gene interaction standpoint. It would suggest in this particular study that adverse drug events are increased by 50% based on drug-to-gene and drug-to-drug-gene interactions. So we're able to provide a greater insight to the clinician beyond just the test result, and they can really utilize as information.

JK : I would like to just go off what Scott just said. This is new technology and the evidence base is growing. That article he was referring to was a May 2014 edition of the publication *Pharmacogenetics*. The study found about 1,000 potential major or substantial interactions in approximately 500 individuals, and found that adverse drug reactions are a major preventable public health type of concern/consideration.

This study elicited that the drug-to-gene interaction or the drug-to-drug-gene interaction—because there are a lot of different interactions that can happen—bring out the importance of doing more studies to generate more evidence to show that these pharmacogenetic testing tools really can assist providers in their management of the

patients with respect to that. From a reimbursement standpoint, it's really important to have evidence to show the value of pharmacogenetic testing, improved outcomes, and demonstrate clinical utility.

3. What are the challenges of pharmacogenetics implementation, and how are different laboratories overcoming these obstacles?

SB : If you look at the growth of this marketplace, a significant amount is in the oncology field. But where you really began to see pharmacogenetics labs take off was back in March of 2010. The FDA put a black box warning on Plavix®, or Clopidogrel, which at that time was the number two prescribed product in the United States.

When I was in pharmacy school twenty years ago—as some of you probably remember—if you put a black box warning on a drug, it was kind of a kiss of death. However, this black box warning suggests that a patient should be tested for 2C19, because Clopidogrel is a prodrug, and it needs to be broken down into its active metabolite.

What we attempted to do at GENETWORx, and what we began to see in this field, were PGx labs beginning to work into a particular specialty. Cardiology became that specialty for 2C19, and many clinicians began to think of it much like the older lab test—if you did a Digoxin Level, you were looking for a Digoxin Level. With 2C19, they began to think of this test as the Clopidogrel test, but it's not. Thousands of drugs get metabolized via 2C19.

The value of the information that can be had is significant. Specialties such as psychiatry and pain management begin to utilize pharmacogenetics. Our approach has been that we can utilize this for 90% of the drugs on the market. Whether it's a pediatric patient, a geriatric patient, or somebody going to their internist—there's extremely valuable information there.

When we're talking about the cost that molecular diagnostics costs today—again, it's your DNA, so it's not going to change. The value of this is the life of the patient. I could reuse that 2C19 or 2D6 Cytochrome P450 metabolic status for that patient for 20 or 30 years. There's significant benefit to the patient.

What we've had to do, because of that gap in knowledge in medical schools and pharmacy schools and so forth, is to turn this into something that a clinician can utilize and value, and change the treatment regimen.

SJH : Having done this testing since about March of 2010, I found that the single most challenging part of this was identifying suitable sample type in order to do all this testing. So when the "Clopidogrel test" came out, physicians were resistant to get a blood draw for just that one particular test; which is funny, because most IVD cleared assays are all blood. But physicians don't necessarily want to do that, so we went to a buccal swab to do the testing.

However, it turned out that the particular swab we were using might be good for one test but not for others, especially for very complex genes like CYP2D6 that cover multiple analytes within one gene. So it took a good amount of time to work out a sample type that could be used to test all the different analytes on the panels.

We also wanted to identify suitable validation materials. That was not easy in the very beginning, but with institutes like the Coriell Institute providing lists of DNA that have the different allele calls on them—that's something that's also helped a lot to bring things along.

JK : As with any new technology or clinical applications, there may be reimbursement challenges. In doing any new technology or any new tests, bringing that on board and adding that to your test menu just in general, regardless of an innovative test like pharmacogenetic testing, you're always going to have a challenge to determine what is a proper coding, what is the coverage, and then what is the payment? Just to understand downstream, how to build your business and what you can anticipate. So I think with respect to this testing, we have definitely seen a shift in the body of evidence to support coverage of these genotyping assays

As laboratorians, you need to have performed the clinical validity for assay development. We've really seen a shift to add on to that consider clinical utility, and that's really just been in the past few years. Payers are looking for outcomes data that shows the value of pharmacogenetic testing improves patient outcomes. This year, we've seen a flurry of activity with respect to molecular testing and Medicare coverage determinations for certain contractors.

So, I do believe we're seeing the shift. And we really need to understand—this will really be our present and future. Looking at clinical utility and reimbursement, or what is the definition of clinical utility; that varies amongst payers. So it doesn't make our job easier. Unfortunately it means that you're going to have to do your homework to understand your payer base. What their clinical utility requirements are—if it's medical necessity, then what's their criteria or threshold? It might mean reaching out to their utilization department or their medical director and really trying to figure that out.

With respect to Medicare, the Social Security Act Section 1862 defines "reasonable and necessary." Well, that doesn't really give us the clinical utility definition. And there have been a few unsuccessful attempts to get the definition of clinical utility in rule making, and those have failed. So we're now at the level of, "okay, what is Medicare's working definition?" Basically, if a test is shown to improve patient outcomes, or has an impact on the treatment of their illness or condition, that's really an operational type of definition they're working with.

4. How does using an FDA-cleared assay simplify the implementation process?

SJH : Well, it really was a very different experience using and implementing an FDA-cleared assay, as opposed to laboratory developed tests. The sheer robustness of the assay, to be honest with you, made it much easier to validate. Before it even gets into our lab, the FDA has to be shown the test can detect what it says it's going to detect and goes through a very rigorous validation. So, by the time it gets to us, if we have those suitable validation materials, it's a much simpler process.

The other part that helped a lot was not just the actual genetics assay, but also the algorithm in the back for generating the data and reporting the results. I think one of the biggest challenges to pharmacogenetic testing is that because a lot of these tests are not FDA approved, the interpretation of what actual results mean as far as what kind of metabolizer you are, and what your therapeutic recommendations should be, are very different.

Every year I do proficiency testing through CAP (College of American Pathologists)—they have a PGx test now—and when you go to CYP2D6, if you see an active and an inactive allele, fifty percent of the labs say that that's a normal metabolizer, and fifty percent say that it's an intermediate metabolizer. It's very disparate. So, the FDA insert has guidelines to help the laboratory make those calls.

JK : In this era of molecular pathology and the Palmetto GBA and Noridian MoIDX Program, we've really seen that an FDA-cleared kit can simplify that process of the technical assessment. McKesson, which requires that if you are a manufacturer, you must have a Z code for your kit. Otherwise, if you're a laboratory developing LDTs and you use ASRs, then the laboratory does that. So for example, if you're a laboratory wanting to utilize the Luminex xTAG kits, there are already Z codes for their two kits. Luminex went through that process and got the Z codes, which now facilitate the process for laboratories putting in for their Z code using the Luminex kit.

Now, let's say if you modify a kit by a simple change of specimen, all you would need to do on that McKesson Z code application is just say, "Specimen type is different from what was in the kit." And that's very acceptable. Laboratories still need to validate the assay; however we've had no laboratories having any issues. So, I think that's just one reimbursement advantage. Because when your Z code is approved, you can actually put the identifier on your claim for Medicare patients.

5. How have the changes in reimbursement affected the landscape?


JK : The recent Medicare local coverage determinations on pharmacogenetic testing have been adopted in several Medicare jurisdictions, to have a broader impact nationally. Certain commercial payers require evidence to support coverage and implement medical policies on pharmacogenetic testing. More labs are generating outcomes data to support the necessity and clinical utility for pharmacogenetic testing and understand the importance of gathering evidence to secure favorable medical coverage policies and reimbursement. At the same time, specialty societies are strengthening their advocacy efforts with both government and private payers.

SB : In the past, when you developed an assay and you had it approved by the FDA, you needed to prove analytical or clinical validity. And now, that has changed to—as Joan was suggesting—clinical utility. So what we are finding is that the payers are kind of making up the rules as they go. How do you prove clinical utility? It hasn't even been defined by this particular Medicare Administrative Contractor. So it's kind of like throwing a dart at a dartboard, and you're not even in the same room, because you don't even know where the dartboard is.

We're seeing a number of hurdles being placed before us. If you're big pharma, and you bring a new product to market, you've essentially got 14 years to recoup your costs. If you're a lab or a manufacturer, imagine bringing your test to the FDA, having it approved, to then find that a payer in the marketplace is dictating that you need to prove clinical utility. Well, how long does it take to prove clinical utility? And prove positive patient outcomes? And who's going to pay for that? And how do you meet these studies?

These are some of the obstacles that we're finding. And in many cases, I think you see commercial payers probably following the government payers in the marketplace. But we're also seeing some commercial payers, who I think are smart enough to recognize the benefits of pharmacogenetics, beginning to do some of their own studies. They're asking us to maybe participate with them, do some pilot programs, do some other things that will support and evidence the fact that this can truly benefit people, and even the payer market side of this as well.

6. How have changes in reimbursement affected the way laboratories perform?

 : It affects it very strongly. We have a panel of CYP450 tests. When a sample comes in, it used to be that you could take that sample and run all the different tests on it, and you would get reimbursed for them. Now, when we get samples in, we have to be very careful from a business perspective that we're only testing samples that we can get paid for. Because, of course, there's technician time, reagent time, reporting time, account registration folks—all those sorts of things that we have to take into account.

So, if we get a sample in and they don't have the right ICD9 code for 2C19, we can't do it. Instead of doing the full panel, we can only do partial panels, and that affects the way the samples get sorted in the laboratory. It also affects the way they get reported out, because it's more difficult for a pharmacist to make a recommendation on a drug if they don't have the whole picture. We have to be very careful about sorting the samples in the laboratory; getting them through and making sure that only the ones that we are testing are being paid for.

7. What is the future of pharmacogenetics testing?

SB : I think we have seen, and are going to continue to see, an outgrowth of a number of things. On the FDA website, they've posted a Pharmacogenetic Biomarker Table.¹ Just a few years ago, there were probably 70 drugs listed there. Now, there's in excess of 155. They range from oncological products to something as simple as Tramadol, as an example, which needs to be activated to its active metabolite.

If you look in the pipeline of drugs coming to market, anywhere from 40–60% of those drugs are specialty drugs. Specialty drugs are defined typically in one of two or three ways. One of which is they work at the genetic level—so, molecular diagnostics. The other is cost. From a payer standpoint, it is very interesting to see that a drug like Kalydeco®, which is manufactured by Vertex Pharmaceuticals for Cystic Fibrosis, only works in a sub-segment of the patient population, and it's very expensive. So, do you think the commercial payer is going to assign that drug to every Cystic Fibrosis patient out there? Absolutely not. But, they don't mind paying, let's say, \$1,000 for that Cystic Fibrosis test to identify that particular patient population.

We see more less-expensive drugs—we'll say Warfarin is one, but it has the most adverse drug events, and because the testing still costs \$100-200, we're seeing payers balk at why they shouldn't cover them. But for these specialty products, that's not necessarily the case.

The other thing that we're beginning to see is when a drug comes to market, more often times than not, I would dare say that almost 100% of pharma manufacturers are investing in biomarker research and/or what we call companion diagnostics. So, the FDA is much more likely to approve a product if it has a companion diagnostic along with it. You can now identify almost a sub-patient population for whom the drug is going to work, whereas we did not have that technology in the past.

If you think about specialty med growth, companion diagnostics—what's the FDA's role going forward? Will they approve a drug or not? Also, I'd say thirty percent of the biopharmaceutical companies out there are doing this on a daily basis. Fifty percent of clinical trials are collecting DNA data now. So we're moving in this direction. And again, GENETWORx got into this business to help the patient. But I think we're going to just see continued growth here. Even though we're experiencing some obstacles, which is something that happens with anything new that comes to market.

SJH : I would say that, from a laboratory perspective, a lot of it depends on the reimbursement landscape. Because if you had asked me two years ago where we would be, I would have said that we would have had a much more expanded panel that covered genes that could be used for a much wider variety of drugs. With the national and local coverage determinations, we have to be much smarter about how we expand our panels. We have to make sure that if we add new markers—which is really the growth of the industry, it's not just for the growth of our company—we have to define markers. But part of finding those new markers is proving the clinical utility. I think probably what laboratories are going to do is bring on new markers, but they're going to have to do additional studies in the clinical landscape in order to get their own local coverage determinations to get those markers paid for.

I see the potential for very expanded panels that will allow pharmacists to assist physicians in treating their patients in a number of different areas. I hope that the reimbursement landscape allows for the continued growth, which I think this industry deserves.

JK : I definitely agree. Reimbursement does impact the future of this testing. And moving forward with precision medicine, we need to consider the payer requirement for clinical utility determination. According to the Clinical Trials government website, currently, there are between 13–15 clinical trials with data that could be published as soon as 2016. So, more and more we're seeing evidence being gathered in the academic settings and private laboratory settings.

There are many different studies that will be performed—there are randomized control trials, there are prospective cohort studies, there are retrospective studies. We need a mix of those studies to help establish coverage based on evidence. That kind of data will benefit really everyone involved in this process. From the patient to the referring clinician to the laboratory performing the test. This evidence will give the payer the knowledge, “how does this testing improve patient outcomes? What is the value of the test?” And that's really what they're looking for. I've been involved in this process quite a lot this year and there have been a lot of coverage determinations coming out; we know the criteria and threshold.

From conversations with a lot of different laboratories, I believe we are moving in a very positive direction. There is an increasing awareness that evidence needs to be generated in the pharmacogenetic space as pharmacogenetic testing is experiencing advancements in the cardiac, psychotropic, and pain specialties. These will then be

great diagnostic tools to assist the clinicians moving forward. And I think we will be seeing a favorable shift for reimbursement as more data is published demonstrating clinical utility.

Pharmacogenetics Innovation at Luminex

Luminex launched its first test to aid in personalized medicine in 2010. Since that time, Luminex has received Health Canada Approval and U.S. FDA clearance, and CE Mark for its xTAG® CYP2D6 Kit v3 and xTAG® CYP2C19 Kit v3 assays, and is a member of the Personalized Medicine Coalition.

For more information on Luminex's pharmacogenetic assays, visit:

www.luminexcorp.com/CYP2D6 or **www.luminexcorp.com/CYP2C19**.

Learn more about the Personalized Medicine Coalition:

www.personalizedmedicinecoalition.org

References

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