Regulatory Matters in Personalized Medicine

How Regulatory Factors can Impact Diagnostics

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Introduction

Regulation of personalized medicine therapies and diagnostics is an essential part of commercialization. Tests have to be approved and it can be a lengthy and complex process. This is made more complicated by the fact that different global regions enforce their own regulatory processes and their guidelines are constantly evolving. It is critical to understand the regulatory timeframes in the early planning stages. Submitting a diagnostic and therapy for simultaneous review can significantly shorten the regulation process and get your test into the marketplace much earlier, but this takes strategic planning and a detailed knowledge of global regulatory procedures in this fast evolving space. More regulatory authorities are moving towards and encouraging co-appraisal, which is a positive development for a well-prepared pharma company.

This Ebook has been created from a selection of our Expert Insights. We hope it will be a useful tool for initiating discussions, creating awareness within your team about diagnostic planning and getting you ready for a future in personalized medicine.

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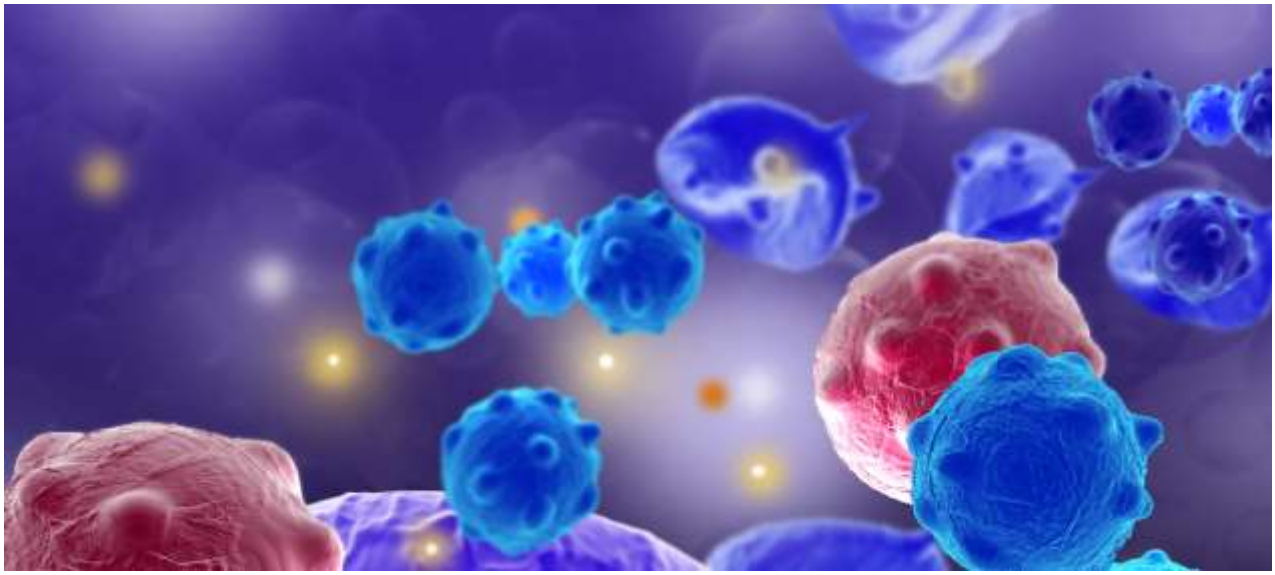
Feedback on IASLC Molecular Testing Guideline for Selection of Lung Cancer Patients – Revision 2016 Draft Recommendations



In August 2016, a team of experts from Diaceutics submitted a response to the IASLC Molecular Testing Guideline for Selection of Lung Cancer Patients, during the public open comment period[1]. Here they share a summary of their thoughts and concerns.

The open comment period offered by the International Association for the Study of Lung Cancer (IASLC) for the Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK gave us the chance to analyse the suggested changes and to put forward our opinion in an area where Diaceutics has industry expertise.

Molecular testing of EGFR and ALK

We welcome the 2016 draft reclassification to a 'strong recommendation' that physicians must use EGFR and ALK molecular testing for lung adenocarcinoma patients at the time of diagnosis presentation with advanced stage disease. It is relevant and appreciated that they include 'molecular testing' of EGFR and ALK, and not just a particular mutation or rearrangement as before. Molecular testing embraces additional mutation testing, which can also cover mutations known to be involved with disease resistance. This is a growing problem facing oncologists as they become more used to ALK inhibitors and new generations of EGFR inhibitors. They are finding many patients not responding at all to treatment or the disease progressing quickly, when they are eligible for the respective treatments for their EGFR mutant or ALK rearranged profile. Resistance mutations are often

present and detectable at diagnosis and some doctors are starting to request this test upfront.

Early testing
We agree it is good to continue to encourage testing in the early stages, but feel the recommendation is too wide. Leaving doctors with the decision to test will, all too often, end up with patients not being tested, for different possible reasons. There may be a lack of time or urgency to treat the patient, the doctor may lack understanding or knowledge around the cost or be concerned about reimbursement. The physician could simply be sticking to protocol and doing what is required rather than recommended, and there could be other factors such as delays in treatment. It will be helpful to see some additional guidance to help doctors narrow the target populations that will benefit from particular testing at early diagnosis, such as non-smokers.

The use of cfDNA
The recommendations regarding the use of cfDNA seem somewhat contradictory. We suggest that 9, 12 and 13 in the analytical section are revisited to clarify the situations in which cfDNA could be tested:

> ***9.*** *There is currently insufficient evidence to support the use of circulating cell-free plasma DNA (cfDNA) molecular methods for the diagnosis of primary lung adenocarcinoma.*
> ***12.*** *In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cell-free plasma DNA (cfDNA) assay for EGFR.*
> ***13.*** *Physicians may use cell-free plasma DNA (cfDNA) methods to identify EGFR T790M mutations in lung adenocarcinoma patients with progression or acquired resistance to EGFR-targeted tyrosine kinase inhibitors; testing of the tumor sample is recommended if the plasma result is negative.*

Turnaround time
With regards to a laboratory turnaround time (TAT) anything beyond two weeks should be considered unacceptable, but this is a personal perception from the clinical standpoint. From the lab operational standpoint, a reduced TAT of less than two weeks is achievable, even for more esoteric or cumbersome techniques. Taking any longer than this is likely to be caused by lab operations not being efficiently managed, and/or the lab batching for economic reasons. In this case, we question if it should be acceptable to keep a NSCLC patient waiting more than two weeks for the result just so that a particular lab can be profitable. There must be a balance between clinical impact and lab profitability.

Responsibility for testing
The responsibility and decision for testing lies primarily with the physician as he or she decides which tests to use to guide therapeutic decisions. However, depending on the amount of sample left, pathologists are in a better position to evaluate the remaining tissues and the possibilities they offer. The role of the pathologist regarding the tests to be performed, and in supporting physicians in their decisions, should not be neglected.

We don't believe that it should be at the discretion of the physician to choose which test has to be used, according to the sample available. It will often be the case that a physician is unaware of sample availability or indeed how much sample is required for a specific test. That should be the responsibility of the pathologist, so in the analytical section 7, instead of *'Physicians should use molecular testing for the appropriate genetic targets on either primary or metastatic lung lesions to guide initial therapy selection*', we would prefer it to say, *'Pathologists should choose the most clinically appropriate sample, either primary or metastatic lung lesions, on which to perform molecular testing.'*

Confirmation by FISH where a result is uncertain

The choice of antibody clone is critical for ALK IHC. Given the lower sensitivity for some clones and in samples with a limited number of tumor cells, we think it wise to recommend confirmation by FISH where a result is uncertain, as is recommended for ROS1 IHC. In the context of ALK (where FISH is used) the proportion of tumor cells is not as important as the number. The current analytical protocol used (Vysis package insert) recommends that in equivocal cases a minimum of 100 tumor cells should be analysed. We believe this is sound practice and that it should be included in the guidelines for ALK and also ROS1.

Interpretation of results

The recommendation that a pathologist should interpret a FISH result is not always practical and will differ between organizations and countries. It is agreed that ultimately pathologists will have the final say, but cytogeneticists or technologists highly trained in FISH analysis and interpretation may have the best understanding of this technique. It is imperative though that if interpretation is to be done by a scientist rather than a pathologist then they should have a thorough training in the identification of tumor cells. If there is any doubt, advice should be sought from a pathologist.

Conclusion

Considering the recommendations overall, Neil Atkey, Director of Scientific Operations at Labceutics, said, "These revised guidelines add clarity to the issues regarding the increasingly important area of biomarker testing in NSCLC. They should enable laboratories to ensure they are offering the appropriate tests for clinical decision-making. A number of details on the use of ctDNA for EGFR testing do, however, need to be harmonised."

NOTE

The CAP/IASLC/AMP Molecular Testing Guideline Public Open Comment Period ran from June 28 to Aug. 2, 2016.
It states: This information is time-limited and does not represent the final content of the Expert Panel recommendation statements. Draft statements are not valid as of August 2, 2016.

**This Expert Insight was originally published in 2016.*

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Amid Regulatory and Reimbursement Difficulties, Some Encouraging Advancements for Personalized Diagnostics

This is the second article in a two-part feature on the state of personalized drug development in which **Turna Ray** discusses the role of labs in personalized medicine, issues for reimbursement and the cost of developing a companion diagnostic.

Back in 2007, when Lawrence Lesko was director of the FDA's Office of Clinical Pharmacology & Biopharmaceutics, he said, “We find more reasons not to proceed with personalized medicine than to proceed with it," summing up the sentiment toward the field at the time. Lesko, who led efforts at the FDA to update the labels of many drugs with pharmacogenetic information, was speaking at the Drug Information Association’s annual meeting, after a particularly discouraging discussion on the reimbursement prospects for genomic technologies.

Seven years later, there are certainly more personalized drugs on the market. In terms of the goal to make precision care mainstream, the field's most boast-worthy accomplishment has been in oncology where molecularly guided strategies—using those multi-gene panels that just a few years ago were thought too complex and expensive—have made their way into most large cancer research centers and are becoming a routine part of care. But there is a long way to go before these tools and strategies are commonplace in community hospital

settings and at local physicians' practices, where more than 80 per cent of cancer patients in the US receive their treatment.

The scientific complexities that seem to deter pharmaceutical firms from investing more readily in the field only increase when one starts looking at diseases outside of cancer. Then, factoring in the difficult regulatory and reimbursement environments, the reasons for not pursuing personalized drug development seem only to have grown since 2007.

The 'forgotten stakeholder'

As far as complexity goes, things can get pretty dicey in the personalized medicine space amid evolving regulations.

The FDA has made it clear that tests intended to help doctors decide whether or not to prescribe a particular drug to a patient need to be reviewed by the agency. However, after years of debate with drugmakers, laboratories and diagnostics firms—each group holding a different view on whether lab developed tests created and performed at a single lab should require the agency's oversight, just as diagnostic kits performed at many labs are—the agency has yet to release a formal plan in this regard. As long as the agency's guidelines on LDTs reportedly remain on hold at the executive branch, FDA-greenlighted predictive tests will continue to exist alongside LDTs that gauge the same drug response markers but don't have the agency's blessing. Against this backdrop, drug developers have been reluctant to openly back the use of LDTs that can not only determine which patients will respond to their drugs, but also so-called complementary tests that can diagnose or gauge the aggressiveness of diseases, as well.

In order for the personalized medicine field to advance, the 'one-drug-one-biomarker-one-test' model that has largely been deployed will have to give way to increasingly complex technologies (i.e., multi-gene panels and next-generation sequencing) that are often performed as LDTs. No doubt, in particularly challenging areas of drug development, for example, in clinical trials investigating PARP inhibitors or DNA-damaging agents, firms such as Clovis Oncology, BioMarin, and PharmaMar are starting to use NGS technologies beyond the biomarker discovery phase, as companion diagnostic panels that will identify best responders to their drugs. Meanwhile, as payers become increasingly focused on reducing health care costs, it's conceivable that complementary tests that, for example, assess when a patient requires more or less treatment, will become a critical part of a patient's treatment paradigm. And this in turn, has implications for the drugs they might receive.

The unanswered questions around FDA's oversight of LDTs gives many drugmakers pause about using, or even publicly talking about using these types of tests more broadly in drug development programs. "I think in any business with regulators, whether its pharma or banking, or anything else, when the rulebook is not incredibly clear, that increases your risk. And businesses don't like risk," J&J's Mark Curran told PGx Reporter of the regulatory uncertainties in the personalized medicine space. J&J last year launched a project to sequence the genomes of 450 rheumatoid arthritis patients who were involved in a clinical trial of its drug Simponi (golimumab), aiming to discover genes that correlate with disease predisposition, as well as new drug targets[1]. For this project, the company is outsourcing the

sequencing to BGI, but J&J does internally use various sequencing platforms to validate external findings.

"We have investments to make and we have to make choices," said Curran, VP of systems pharmacology and biomarkers in the immunology therapeutics area at J&J's Janssen Pharmaceuticals. "We want to make sure that we first do what's right for patients and then that we get a return on the investment, [and] that we're actually able to launch and tell people about these wonderful new products when they come to be."

Having followed FDA's advice, and when it's time to launch a personalized therapy alongside its FDA-approved companion test kit, drugmakers run into the problem of having to convince labs that may already be running their own LDTs to adopt the kit. Some labs have been performing their own internally developed genetic tests for years, and integrating a new kit impacts workflow and costs.

Pharma companies have done a poor job educating and incentivizing labs that run these companion kits, believes Peter Keeling, CEO of personalized medicine-focused consulting firm Diaceutics. "The laboratory is the forgotten stakeholder," he said. "We were doing some work around BCR-ABL testing in Europe, and the general mood of the laboratories is that they are angry. They are angry that they're being asked to run these tests without a lot of help on where they will be used and with sorting out reimbursement. They're having to do that themselves."

Through a division called Labceutics, Keeling and his colleagues are trying to increase adoption of personalized medicine by facilitating the broad availability of companion tests across the 14,000 labs in the EU that operate in a decentralized fashion. An example of the kind of work Labceutics does is the project it launched last year with Asuragen to track how variable BCR-ABL testing is across European labs[2]. One of the key takeaways of that survey was that despite the availability of BCR-ABL test kits, the surveyed labs usually default to an LDT.

BCR-ABL testing is more a complementary, rather than a companion, diagnostic. By periodically testing BCR-ABL transcript levels doctors can track if a chronic myeloid leukemia patient is relapsing or maintaining remission, key determinations that influence treatment strategy. Asuragen and Gleevec sponsor Novartis inked an exclusive agreement in 2010 to develop calibrators and laboratory software reporting tools, which they hoped would help labs standardize BCR-ABL testing[3].

Even if drugmakers are reluctant to invest in an LDT from a companion diagnostic standpoint, Keeling recommends to his pharma clients that they partner with labs to standardize methods for sample collection and complementary testing. He is planning to launch a Labceutics network in the US as well, where drug developers have similarly struggled to convince hospital labs to adopt an FDA-approved kit over their own LDTs. An example of this was when Roche launched its personalized melanoma drug Zelboraf (vemurafenib) with a companion kit that picked out best responders with BRAF-mutated tumors[4].

Industry players are hoping that long-awaited LDT regulations from the FDA will help smooth many of these tensions in the field. When the agency released a final guidance on marketing research-use/investigational-use only IVD products however, it didn't necessarily align the views of disparate players in the personalized medicine space—the entities that were always against greater FDA regulation maintained their opposition—but at least there is now less doubt about the agency's expectations and regulatory intentions, which is some progress[5].

Additionally, the FDA recently cleared the first next generation sequencing platform, Illumina's MiSeqDx, and many in the industry believe this provides a framework for other NGS-based tests to go through regulatory approval or clearance. With this clearance, the agency said it hoped that labs previously using Illumina's MiSeq research-use platform to develop internal lab tests, would now run their LDTs on the FDA-cleared platform. At least one drug developer so far, Amgen, has announced it would develop a companion test using MiSeqDx for its pharmacogenetically targeted colorectal cancer drug, Vectibix.

"There is a misunderstanding that it has to be either a lab developed test, or an FDA-approved kit. It's not a this or that," Lakshman Ramamurthy, director of FDA Regulatory & Policy at health care strategic advisory firm Avalere Health told PGx Reporter. "Drug companies are hamstrung by the fact that in order to seek a companion testing claim they have to come to the altar holding somebody's hand," said Ramamurthy, formerly a senior reviewer and policy advisor at FDA's diagnostics division. "Is a clinical laboratory willing to do that? Some labs may be willing to but don't forget, many labs cannot pursue that path from a financial standpoint."

Read the full article at http://www.genomeweb.com/clinical-genomics/amid-regulatory-and-reimbursement-difficulties-some-encouraging-advancements-per

**This Expert Insight was originally published in 2014.*

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New Device and Diagnostics Legislation Could Shake Up the Drug Industry

Patrick Considine comments on the 2013 proposals by the European Parliament's Health Committee to introduce new legislation for devices and in vitro diagnostics.

This month [September 2013], the European Parliament's Health Committee will reach its view on the two major proposals launched last year by EU officials — one on devices, and one on in vitro diagnostics. In October, the parliament as a whole is due to agree its definitive opinion on the proposals. And before the end of the year, the governments of the EU's 28 member states are expected to finalize their position on the proposals, too. So by early 2014, new rules should be signed off that will change the face of EU controls on these products[1].

If the proposals are passed, a number of changes impacting regulation of IVDs in the EU will be introduced:

> The IVD Directive would be replaced by IVD Regulations. EU member states have interpreted and implemented the current directives in different ways, which led to

different levels of patient and public health protection in the European Union and created obstacles within the single market. The draft EU Regulations, which are laws unto themselves, do not need to be transposed into law within each member state, as is the case for directives.

The proposed Regulation introduces a new risk-rule classification system based on the Global Harmonization Task Force (GHTF) classification rules which will impact the review requirement for all IVDs. Under the current IVD directive (98/79/EC), approximately 80 per cent of IVD products are grouped in the self-certification class. In the proposed Regulation only 20 per cent of IVD products will remain in the self-certification category, while a form of third-party pre-market intervention will be required for the remaining 80 per cent of products. All 'human genetic testing' falls into Class C. This will set a higher bar for device manufacturers than the current self-certification system. Manufacturers of Class C devices will have their quality management systems inspected by national Notified Bodies. This will make approval of IVD products more expensive and slower.

The exemption from the regulations for devices manufactured and used within the same health institution (LDT) is retained, but is now restricted to health institutions compliant with ISO 15189 or other equivalent recognized standard. Labs which are not accredited would only be allowed to use CE-marked tests.

**This Expert Insight was originally published in 2013.*

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Regulated and Disseminated: A Way Forward for LDTs

Ron Mazumder of Janssen Diagnostics discusses how laboratory developed tests offer pharma an opportunity and comments on how risk can be minimized and how they could be used alongside in vitro diagnostics.

Laboratory developed tests (LDTs) have proliferated throughout the diagnostics industry and the centralized reference lab has become a significant channel through which certain content can be delivered. Because these LDTs have not historically been subject to the same regulations as in vitro diagnostic tests submitted to the FDA, many LDTs may not have undergone rigorous analytical and clinical validation, potentially leading to precision and accuracy issues. Indeed, a recent external quality assessment has shown that, among 59 laboratories in Europe which used their own preferred method for DNA isolation and mutation analysis, only 69 per cent of laboratories correctly identified KRAS mutational status in all ten samples used in the assessment[1]. This situation has led to the 2008 filing of a citizen petition by Genentech to the FDA considering implementation of a risk-based oversight of LDTs[2], and numerous comments by diagnostics manufacturers on the companion diagnostics draft guidance issued in 2011.

If the playing field were leveled and LDTs were submitted to the FDA through the pre-market approval (PMA) process (or whatever classification is appropriate, given the risk), there could be several advantages for pharmaceutical developers. First, because the design verification and manufacturing validation timelines are typically shorter for a LDT relative to what is required for a disseminated kit, predictive biomarkers identified late in therapeutic clinical development could still be implemented as an Investigational Use Only (IUO) device at the start of Phase 3. Second, the LDT PMA could eventually be incorporated into a disseminated kit format (i.e., tech transfer), offering a larger commercial channel at drug launch.

How could such forces alter the diagnostics landscape? Some large diagnostics companies may embrace multi-faceted approaches (LDT and kit) to deliver diagnostic information. The flexibility offered by such approaches would not be lost on pharmaceutical developers requiring a companion diagnostic.

**This Expert Insight was originally published in 2012.*

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BRCA Testing: Will the US Supreme Court Judgement Make A Difference?

A disclosure by the actress Angelina Jolie that she carries the ‘faulty gene’ that can lead to breast and ovarian cancer has raised the profile of BRCA testing, while a US Supreme Court judgement means that Myriad Genetic Laboratories is no longer the sole provider of BRCA testing clinical services. **Patrick Considine** suggests that ASCO/CAP should now play a leading role in ensuring the accuracy and precision of BRCA testing, as it has done previously for HER2 testing.

BRCA1 and BRCA2 are human genes that belong to a class of genes known as tumor suppressors. Mutation of these genes has been linked to hereditary breast and ovarian cancer. A woman's risk of developing breast and/or ovarian cancer is greatly increased if she inherits a deleterious (harmful) BRCA1 or BRCA2 mutation. Men with these mutations also have an increased risk of breast cancer. Both men and women who have harmful BRCA1 or BRCA2 mutations may be at increased risk of other cancers. Current estimates are that about one in 1,000 women carry a BRCA mutation and that inheritance of BRCA mutations accounts for five to seven percent of all breast cancer.

To establish a person’s risk of developing breast or ovarian cancer a genetic test is carried out to check for BRCA1 and BRCA2 mutations. The clinical value of BRCA testing was headlined recently [2013] by the disclosure from actress Angelina Jolie in The New York Times: "I carry a 'faulty' gene, BRCA1, which sharply increases my risk of developing breast cancer and ovarian cancer."[1] Jolie, whose mother died of breast cancer, said she chose to have her breasts removed to reduce exposure. The high profile disclosure has led to unprecedented requests for BRCA genetic counselling and testing.

Until the Supreme Court judgement, Myriad Genetic Laboratories held the patent on the BRCA genes and was the only commercial laboratory in the US to test for BRCA mutations in the general population. The ruling is in part a victory for a group of scientists and patients' rights advocates that argued Myriad's patents chilled scientific research and hampered access to affordable genetic risk screening. The cost of Myriad's BRACAnalysis test in the US varies somewhat by payer but is generally in the $3,000 to $4,000 range. Currently, BRACAnalysis testing accounts for a striking 88 per cent of the company's nearly $400 million in annual revenues, with only 2 per cent of those sales occurring ex-US.

The judgement will allow the market to open up so that other laboratories can offer the test and that should make the test less expensive and more available to more women. Already a number of laboratories have signalled their intention to offer BRCA testing. Within hours of the decision, the University of Washington and Ambry Genetics said they would immediately offer expanded testing that included BRCA1 and BRCA2. Quest Diagnostics, one of the largest commercial laboratories in the US, announced "we now intend to validate and offer a BRCA1 and BRCA2 test service to physicians and patients later this year." Others include DNATraits, part of Houston-based Gene By Gene, Ltd, which said it would offer BRCA gene testing in the United States for $995, less than a third of the current price.

Myriad, despite its critics, is considered as generally doing a good job by most physicians, with BRACAnalysis considered to be the best BRCA gene test on the market. Myriad has several competitive advantages based on its long experience in BRCA testing. It runs a highly efficient laboratory, has developed a network of health professionals who use its services, has secured agreements with hundreds of payers, has brand recognition based in part on direct-to-consumer advertising, and has a trained sales force.

However, Myriad's proprietary Variants of Uncertain Significance (VUS) database, which records rarely-occurring mutations within the BRCA gene and reduces the number of uncertain test results, may give Myriad a strong competitive edge. Myriad has amassed its database of thousands of sequences of the two genes and correlated mutations in these sequences with risk-estimate indicators based in part on the medical histories of the patient and her family members. At first, the company freely shared this information by contributing it to public databases that researchers and clinicians could access. But in 2004, Myriad stopped these contributions, saying the potential was too great that the Myriad sequences were being used to generate inaccurate risk estimates for patient.

The key driver of demand for an alternative to the BRACAnalysis test will be determined by whether Myriad allows public access to its database. "While some US physicians have shown interest in reconstructing their own Myriad VUS databases from patient reports, this fragmentary effort would likely take a long time. The Supreme Court's decision therefore seems unlikely to change the status of Myriad's BRACAnalysis as the test of choice for hereditary breast cancer gene testing in the US, thanks to this VUS database," says Dr. Thompson (GlobalData's senior analyst covering in vitro diagnostics).

Myriad customers have joined forces with geneticist Robert Nussbaum, MD, of UCSF, to do an end-run around the company's vast database. In Nussbaum's Sharing Clinical Reports

Project, clinicians and patients around the country are encouraged to submit the reports generated by Myriad for each patient. The reports contain valuable information about mutations and risk estimates. Alone, each report is useful only to the patient for whom it was generated. But if enough patients and researchers were to submit the results, the project could begin to reconstitute the database Myriad now keeps under lock and key. Nussbaum estimates that within a year researchers will have access to enough high-quality data to render Myriad's head start unimportant. Stanford big-data expert Atul Butte, agrees that the landscape for genetic diagnostic testing is likely to change rapidly as a result of this week's events. "I think the community is eventually going to end up with a resource that's even better than what Myriad has. Myriad may know better than anyone else what the natural variation is in these genes. But the true value lies not just in knowing what the variants are, but how they connect to clinical disease. If the research and clinical community do this right it will be able to connect the sequences directly with patient outcome and generate more-meaningful results."

Now that a number of laboratories will be providing BRCA testing clinical services, the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) should play a leading role in ensuring the accuracy and precision of BRCA testing through the development of guidelines, recommendations and a proficiency testing program as they have done for breast cancer HER2 testing.

**This Expert Insight was originally published in 2013.*

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