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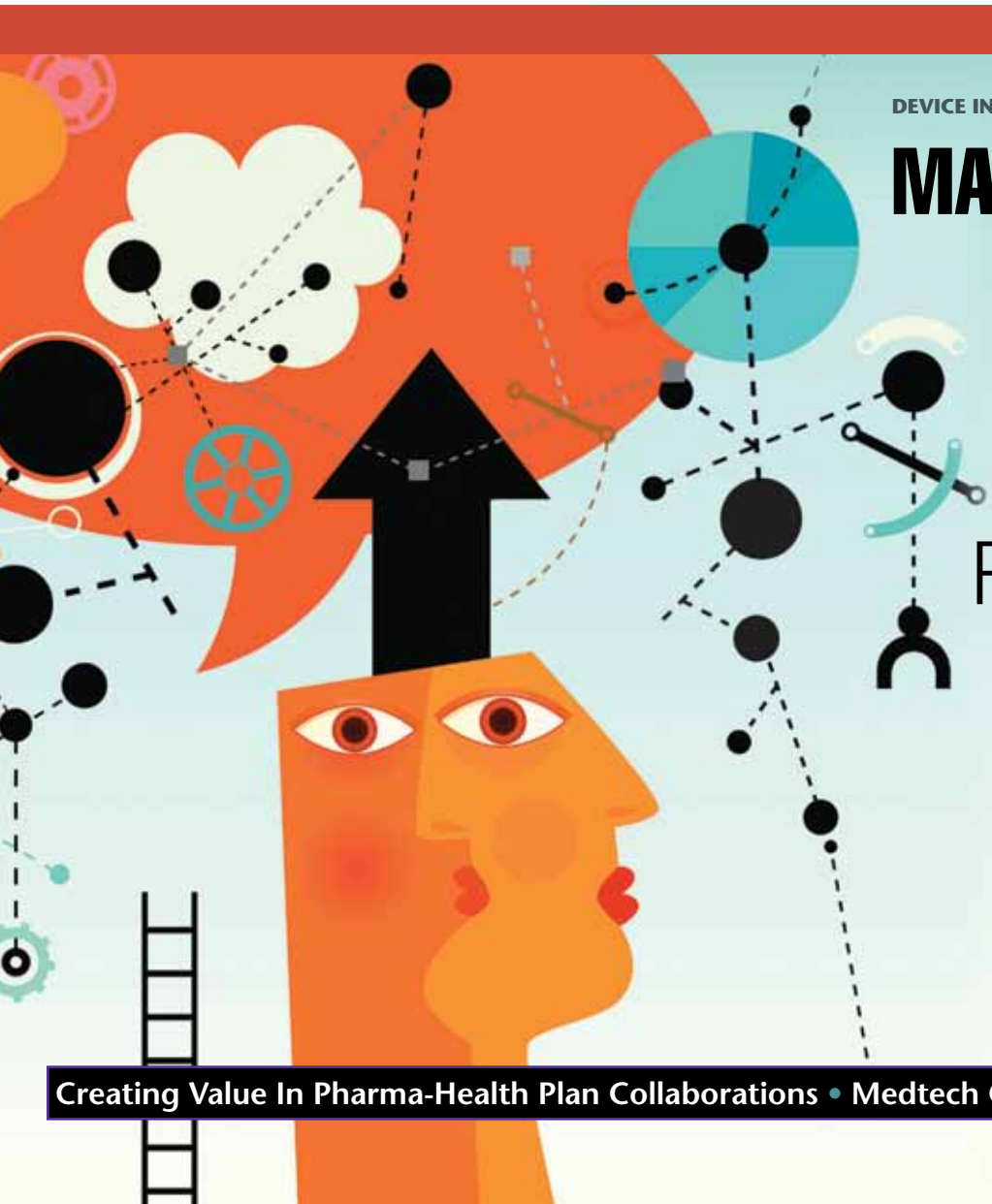

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VERACYTE: How To Build A Molecular Cytology Company

The company has launched a complex molecular diagnostic test in thyroid in record time and with impressive capital efficiency. Veracyte could be a model for high-value diagnostics, especially if it can successfully adopt its approach in a broader market.

- Veracyte is focused on addressing unmet diagnostic needs preoperatively, and resolving the ambiguity that often results from cytology. It aims to avoid unnecessary surgery, substantially reducing medical costs for the health care system.
- Market focused, the company made the decision to develop its first product, a gene expression classifier that shows whether indeterminate thyroid biopsies are benign for cancer, even before settling on the technology platform it would adopt.
- Veracyte is co-promoting the thyroid test with Genzyme. Its whole genome discovery approach could also lead to identification of new drug targets or further diagnostic targets, potentially opening up partnering opportunities with a pharma company.
- Next on Veracyte's list of indications is lung disease, reflecting many of the same clinical priorities. A second program in a bigger market could make it an attractive IPO or M&A candidate.

BY MARK L. RATNER

The molecular cytology firm **Veracyte Inc.** arose in 2008 out of Calderome, an incubator formed by West Coast venture capital firms Kleiner Perkins Caufield & Byers (KPCB), TPG, and Versant Ventures. As they did with their other endeavors in molecular diagnostics in the 2000s, the VCs emphasized the need to understand the pharmacoeconomics of a potential new diagnostic test early on and to have a clear vision of how the test could influence clinical decision making.

Veracyte held to these founding precepts in deciding on its first clinical program, the development of a complex gene expression signature that would tell endocrinologists whether thyroid nodule samples indeterminate by cytology (the process of looking at cells under a microscope to detect abnormalities) are benign for cancer, thereby avoiding unnecessary thyroid surgery. But Veracyte also set other criteria, which have enabled rapid and capital-efficient clinical test development. Taken together, they form a model for how to build a company in today's molecular diagnostics space.

INCUBATING THE CONCEPT

Along with identifying a business opportunity for using molecular tools that would influence diagnostic decisions and lower health care costs, the VCs wanted to avoid cases where the physician deciding whether to use a test was also the one most adversely affected by that decision. That can be tricky, says TPG's Fred Cohen, MD, given that half the costs across the health care system are personnel related. "No matter what we do, there are no free rides in making the system more efficient," he says. "When we were doing CardioDx we were focused on how we could save money for the system but less focused on who would be losing money in that process," Cohen explains, referring to **CardioDx Inc.**, a mid-2000s start-up founded by TPG and KPCB. (*See "CardioDx: Bringing Molecular Diagnostics Into the Cardiovascular Arena"* — IN VIVO*, March 2010*.) By the time Calderome incubated Veracyte, however, the VCs were focused more on the question of who would be losing money and where were they in the decision tree, because if the savings were downstream of the person ordering a test, it would be easier to gain adoption – a new facet in looking at how an innovation can disrupt workflow.

Even with this informed perspective, a track record of company formation, and a glut of potential clinical ideas around which to build a company, Calderome still needed to formulate a solid business plan connecting these elements. Bonnie Anderson, now Veracyte's CEO, had joined the incubator as a consultant in July 2007. "They basically gave me the goal of having a business plan to fund a company by the end of the year or we would probably shut the incubator down," she says. By the end of 2007, Anderson had carved out a plan for what would become Veracyte.

"I think one of the perspectives I brought

to Calderome was to really focus on how to address the market and the customer," says Anderson. With the aim of starting a single company, Calderome had mapped out at least a half dozen possibilities and did various levels of assessment on each: understanding how patients move through the process of diagnosis and treatment and picking the best way to intersect with that, and making sure the market was right-sized for a new company to target. The incubator also thought long and hard about devising the right question that would resolve the unknown factor driving the clinical need, and then about if it were to address that question, how easy would it be to do a clinical trial to establish that a test works well. "We spent a lot of time thinking about what a trial needed to look like," says Anderson, especially in regard to devising a test that would give a clear and definitive diagnosis that answered a specific clinical question.

Another factor kept popping up out of Calderome's examinations of unmet needs in various clinical situations: the realization that when a cytology sample was involved up front, there was a much greater amount of inherent ambiguity, repeat procedures, and cost that could be avoided if you could improve that cytology sample result. "Every time we looked at what happened next with the patients, there was a ton of ambiguity," says Anderson. "That's what set us out to say we were going to pioneer a new field of molecular cytology."

PRIORITIZING THYROID

Calderome focused the company's strategy upstream of surgical sample evaluation to address any ambiguity created by indeterminate cytopathology results. "If the patient has gone to surgery and you have a surgical tissue sample to develop your test around, it's way too late to be diagnosing," says Anderson. With those considerations in mind, thyroid nodule testing quickly bubbled up to the top of Veracyte's list of potential indications.

When a thyroid biopsy is indeterminate by cytopathology, it is delivered to an endocrinologist, who usually refers the patient to surgery for a complete or partial thyroidectomy. "When we looked at what happens next with the patient, we saw this pool of 100,000 patients with indeterminate results now being part of a surgical pool," says Anderson. So the only way to change clinical practice – referral to surgery – is to answer the question of who is benign, not who is malignant. For the same reason, it became clear that the only clinical parameter that made a difference in decision making was having a test with a high negative predictive value. That took away any debate as to the kind of performance characteristic a test should aim for in advance of developing the product. Looking for "benignity" also reinforced that the setting for the test was early in the diagnostic process – before involving a surgeon, as so often happens early in diagnosing cancer.

In short order, Veracyte nominated thyroid as its lead program. "It had the least amount of risk as our first indication to market," says Anderson. The unmet need was compelling and the market was easily addressable for a small company, given that with the endocrinologist there was a single specialist who handled almost all aspects of patient care. And the company made that decision even before considering the platform technology it would use. The assumption was that with the richness of genomic information that could be collected, "surely we would find a technology that could do the job," Anderson says.

"The thyroid nodule molecular cytology approach checked the box of an ever-increasing list of boxes you needed to check," Cohen adds. With the array of genomics tools available at the time, Veracyte believed that using microarray technology to look at the whole genome and develop out of that a complex and unbiased gene expression signature was scientifically feasable. Because endocrinologists refer patients with indeterminate or suspect nodules for surgery but do not actually do the procedure themselves, a test that told them a nodule was benign avoided the issue of making the decision maker the one most adversely affected by the decision. And the endocrinology market is one where a relatively small sales force could effectively market to the target audience.

By all accounts, Veracyte's *Afirma* thyroid test, which launched in early 2011, has exceeded expectations to this point.

Afirma's major selling point is its high negative predictive value (NPV, the measure of a test's sensitivity), which means there's only a small chance that an indeterminate nodule called benign by Afirma is cancer. If Afirma therefore can help make decisions about which patients do not require an expensive surgical procedure, "they really have a nice case," says Jorge Leon, PhD, principal at the consultancy Leomics Inc. He analogizes to the development of a molecular test for human papilloma virus (HPV), the cause of nearly all cervical cancer. "It's very similar to what HPV did for ASCUS [atypical squamous cells of undetermined origin] in the '80s and early '90s," Leon says. HPV testing was positioned as a way to help sort out indeterminate or suspicious Pap smears: an HPV negative meant patients did not have to undergo colposcopy.

Looking for "benignity" also reinforced that the setting for Veracyte's test was early in the diagnostic process – before involving a surgeon, as so often happens early in diagnosing cancer.

Leon had identified a gene expression signature from the **National Institutes of Health** for diagnosing thyroid in 2006, which he presented to the **Mayo Clinic College of Medicine** for licensing. "I thought mRNA expression for thyroid was one of the best opportunities in diagnostics," he says. But Mayo did not want to dedicate sufficient resources to build a product. He similarly approached **Quest Diagnostics Inc.** with the concept, also to be turned down. "Veracyte is illustrative of one of the megatrends in the industry," he says, that "new genomic and clinical genomics products are much better served by start-ups that have the right funding and the right focus to do the job."

Leon falls short of saying that Afirma is the best thyroid gene expression signature ever devised, but having the absolute best test is not always the prerequisite for commercial success. "Is Genomic Health's *OncotypeDX* the best signature for breast cancer?" he asks. "Clearly not, and that's understood." But **Genomic Health Inc.** did a good job of packaging that information, validating the test, and

getting endorsement from the National Comprehensive Cancer Network (NCCN), the Centers for Medicare and Medicaid Services, and private payors. Similarly, Veracyte has had the results from an extensive prospective, blinded, multicenter study of Afirma published in the *New England Journal of Medicine* (*NEJM*), has received a recommendation in guidelines for thyroid cancer diagnosis from NCCN based on the test's published NPV (95%), and has the endorsement of Medicare.

To gain adoption of such tests, "you need a tremendous amount of clinical utility data," says Leon, to be able to show the value of a product in the overall context of the tools doctors use to manage their patients. "Veracyte did that, and in half the time and with half the money of Genomic Health."

With 20% to 25% of thyroid FNAs indeterminate, Leon estimates the market opportunity at between 70,000 and 90,000 cases, of which the company "can probably easily capture half," he says, at an average paid test price he ballparks at $2,000 (the non-contracted price of the test is just over $4,200). So Veracyte could generate $70 million to $140 million, Leon calculates. "That's pretty good," he says. "They can reach those numbers pretty quickly because of the NCCN guidelines."

Afirma's rapid development is testament to the company's efficient use of capital and disciplined planning. Veracyte had certain benchmarks set by other successful companies they have constantly tried to beat, Cohen says. In terms of reimbursement, "they are on the fastest trajectory we have seen," he says. "They were anxious to be a reference company and do at least as well or better than best practices. I think that's driven the company to be more capital efficient and time efficient."

Veracyte launched the test in its CLIA lab two years and nine months from company formation, exceeding its original plan by six months. Adoption of Afirma has also ramped up faster than expected, with FNA sample volume about 20% higher than Veracyte had anticipated for year one. Plus, Medicare coverage was awarded more than a year earlier than other companies had experienced with similar products – Afirma was one of only two molecular diagnostic tests given a favorable technology assessment under Medicare contractor Palmetto GBA's MolDx (Molecular Diagnostic Services) program, which covers California, where Veracyte has its CLIA lab. (*See "The Balkanized State Of Molecular Diagnostics Reimbursement"* — IN VIVO, *November 2012*.)

ANALYZING THYROID NODULES

Patients found to have thyroid nodules are almost universally referred to an endocrinologist for follow-up. If after blood work and ultrasound on the nodule the features look suspicious, the endocrinologist will sample the nodule by taking a fine needle aspirate (FNA, the biopsy performed to gather a sample for cytology) of the tissue. About two-thirds of cases are found to be benign and most of those can be managed conservatively. But 20% to 25% are cytologically indeterminate, and as a general rule, when that happens, patients are recommended for surgery for diagnostic accuracy.

Cancerous, suspicious, and even indeterminate nodules are removed with a complete or partial thyroidectomy, after which patients will be on lifelong hormone replacement therapy, also managed by the endocrinologist. Half of middle-aged women and about a quarter of middle-aged men have a thyroid nodule. Approximately 5% of thyroid nodules are cancerous.

In cases of benign nodules, the endocrinologist will continue to manage the patient and decide on treatment and follow-up. This differentiates thyroid from other cancer indications, where a stream of specialists may be making decisions around patient care. Because a specialist ultimately has 100% of the patient care in his/her hands, thyroid is an easier market to address.

Thyroid diagnosis is also a good market to serve with a specialty lab. There are about 3,000 endocrinologists in the US who do thyroid FNAs. They collect the FNAs in their office and send them off to a commercial lab, unlike many other samplings in cancer, where a tissue sample is taken in a surgical suite in a hospital, and automatically sent to the lab at that institution.

That's not to say that Veracyte did not face development challenges. Whether the amount of material one gets from an FNA was sufficient to generate an RNA expression signature reproducibly for clinical practice was unknown. "One of the key lessons of Veracyte for me was that you can work with very small samples and come up with clinically useful information, which means basically that you can do molecular cytology," Cohen says. "Before starting Veracyte, that was not a given."

TECHNOLOGY? NOT A PROBLEM

The company did know it wanted to follow a whole genome, unbiased approach to biomarker discovery, because to answer biological questions across eight subtypes of thyroid diagnoses, it needed a substantial number of genes to be able to accurately segregate the benign nodules from those that were suspicious for malignancy. (The Afirma test uses 167 markers: 142 genes, plus an additional 25 supplemental genes used to improve classification of rare cancer subtypes.)

A whole genome approach says that although we may not really know which genes are fully involved in all the complexities of a thyroid cancer or a benign process, that doesn't matter. Because by looking at all 22,000 genes in the cells, a pattern will fall out that can be used diagnostically. Researchers can also look at what fell out of the pattern and work backwards into the laboratory. "It has shaken up the discovery paradigm," says Erik Alexander, MD, of **Brigham and Women's Hospital**, co-principal investigator on Veracyte's prospective trial of Afirma.

"I was confident a signature could be developed," says Chief Scientific Officer Giulia Kennedy, PhD. It was just a matter of getting the right samples, she says, to be able to reflect the subtle heterogeneity within phenotypes.

"We can get deep transcriptional or DNA information from the sample quite easily," Kennedy says. "The challenge is pairing this with an appropriate depth of clinical information." Good bioinformatics is critical, because to solve the problem of matching clinical features with genomics data you need to collect very extensive clinical information. Since information on individual patients may not be standardized or abundant, it tends not to be high dimensional and is difficult to cluster. "You really need to push to understand the subtle phenotypes of your samples

and spend time annotating them in great detail," explains Kennedy.

Jorge Leon credits Veracyte as one of the specialist molecular diagnostics companies to emphasize this capability. "This is where I give them a lot of value," he says. "The big companies don't realize that when looking at 90 or a 100 genes, the bioinformatics software is the most powerful piece of a test, to be able to make calls all the time."

Microarray technology fit the bill as a platform for the initial analysis, and Veracyte continues to use arrays as its commercial platform in its CLIA lab. The decision was borne out of Kennedy's experience at **Affymetrix Inc.**, where she helped build its whole genome SNP chip offerings. "I had designed several custom arrays and knew the power of being able to keep the same probes on a custom array that was just smaller and cheaper. I think we saved a lot of time and effort." Plus, Veracyte could continue to train the algorithm while doing a lot of the analytical work to develop the assay.

THE NEXT HURDLE

After it decided on thyroid as a first program and began biomarker discovery, Veracyte developed a roadmap to market, basically setting a date when it would launch the test and working backwards from that, allocating the time needed for discovery, development, validation, and getting the diagnostic ready for commercial use in its lab.

But choosing to develop a test on a tiny sample collected as an FNA – its aimed-for core competency – proved problematic early on because sample collection was not as straightforward as had been anticipated.

The first step for Veracyte in developing the gene expression signature (or classifier) in thyroid was to prove that it could use the classifier to segregate benign from malignant in thyroid tissue. To do this, Veracyte took tissue from patients whose thyroids have been removed, representing the different biologies in those patients. The company then moved to FNAs.

The original plan was to purchase FNAs that had been stored in retrospective banks at some of their academic collaborators. "We thought we'd go and purchase 300 of these FNAs after we have feasibility in tissue and evolve our classifier to work on FNAs," Anderson says. But much to their surprise, the Veracyte team members discovered that the samples they acquired had been so poorly preserved that they could not make sense of the genomic information. "At that point, we realized we would have to prospectively go collect FNAs so we could preserve them and handle them in a way in which we were in control of the samples," says Anderson.

Moving to prospective collection ended up strengthening the level of evidence. "It helped us in the long run," says Chief Medical Officer Richard Lanman, MD. With a five-person clinical trials resources team, Veracyte expanded the number of clinical sites to 49 over two and a half months, with nearly 5000 samples ultimately collected over two and a half years for the validation trial. "There is no thyroid neoplasm study of that size ever done, period," Lanman says. But having control over the data and sample quality greatly outweighed the risk of developing a test based on lesser sample integrity and clinical data.

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LAUNCHING AFIRMA

In October 2010, Veracyte launched Afirma to a select group of academic thought leaders that had already been collaborating on the prospective clinical study. Then in January 2011, starting in Florida and Texas, it officially launched to community-based endocrinology practices, the portion of the market where the majority of patients have FNAs taken.

"Most of the FNAs are done in the community market and most of the opportunity to improve patient care is in that segment," says Chris Hall, Veracyte's chief commercial officer. Veracyte also offers the test to academic medical centers, which run the cytology under their roof and store and send samples to Veracyte when a call is indeterminate.

Veracyte decided that the best way to serve the community market would be to have an endocrinologist use a single Veracyte-designated lab, Thyroid Cytology Partners (TCP), for initial examination instead of a local cytologist. "We had to deliver this in a model that made it easy for physicians to offer and deliver the product to their patients the first time they do an FNA on that patient," Hall says. The standard TCP one-stop-shop procedure would least disturb physician practice, but at the same time take into account the vagaries of cytology, assure the quality of sample collection, and standardize the process.

An endocrinologist takes an FNA (usually performing four to six passes to gather the cells) and packs the samples for shipment to Veracyte, with one vial labeled for TCP to read and another for possible analysis at Veracyte. Veracyte prepares slides for analysis using the microscope and ships them to TCP, while storing the other vial in case the cytopathology is indeterminate and the Afirma test is needed. TCP's volume from Afirma sales has increased from several hundred in the first quarter of 2011 to nearly 10,000 in the fourth quarter of 2012, according to Veracyte, with steady growth during that time. In total, FNA volume under the Afirma protocol was more than 32,000 as of the end of 2012. Out of those samples, along with indeterminate samples sent from academic centers, Veracyte has conducted more than 6,500 Afirma classifier tests. The rate of indeterminate FNA results for TCP is between 15% and 20% according to Veracyte, which is on the low side of the 15% to 30% that appears in the literature. Afirma produces a benign result in approximately 50% of these cases.

Using Afirma, Veracyte is also identifying some rare types of thyroid cancer that are difficult to diagnose with the microscope but are obvious genomically. The main Afirma classifier makes a call of either benign or suspicious for malignancy. The chip also contains additional genes that can potentially be used to identify these rare cancers and guide therapy in a variety of ways.

A nodule called suspicious for medullary thyroid cancer, for example, would require aggressive surgery. A metastatic

kidney or melanoma tumor might also show up in the thyroid: under the microscope it's hard to tell that such a tumor is not thyroid, but it's obvious using genomics. In that situation, the physician wouldn't operate. "If someone has kidney cancer metastasized to the thyroid, the thyroid is the least of their problems," says Lanman. Veracyte is looking to add this kind of supplemental information to the Afirma chip and algorithms, but has not yet validated this use. For now, it simply alerts the physician that a rare condition may exist.

By the time Afirma launched, Veracyte was in the midst of negotiating a co-promotion and global marketing deal with **Sanofi**'s **Genzyme Corp.** As a player in thyroid cancer follow-up treatment with the drug *Thyrogen* (thyrotropin), Genzyme had been aware of Veracyte through its mutual clinical academic collaborators. Genzyme was also looking to expand its portfolio.

"We canvassed the industry for this type of product," says Alicia Secor, VP and general manager, endocrinology, at Genzyme. "This was the best comprehensive offering," she says. Other mutation panels, such as **Asuragen Inc.**'s microRNA-based *miRinform* thyroid test, use only a handful of predictive markers taken from the literature, and are limited in scope.

"They are the experts in laboratory services, laboratory developed tests. We are the experts in thyroid cancer," says Secor. But the partnership is not necessarily about thyroid cancer – it's about improving thyroid management. "It is pulling us further out into the community endocrinology arena," she says, which is helpful to Thyrogen. On the flip side, building a sales force is hard for a new, small company and Genzyme offered cost-effective global reach.

Ex-US, Veracyte expects initially to consolidate samples for local cytopathology review at academic centers, with indeterminate samples submitted for testing at Veracyte in the US – a similar model to what is done in US academic centers. It believes that over time, larger markets may be able to support a regional laboratory investment, but in the meantime, the company will meet the needs of physicians and patients internationally using routine shipping to its existing CLIA facility.

Applying the CLIA model – eschewing the development of an in vitro diagnostic (IVD) kit distributed to many labs in favor of having samples shipped to a specialty lab for analysis – is often questioned as a global strategy. "The only criticism I have of the Kleiner Perkins/Genomic Health model of doing everything under the same roof is they are too US centered," Leon says. "There is another market that is three times bigger and the only way to reach it is through a device and not FedEx or UPS."

However, in the case of thyroid nodule testing, the workflow argued against kit development. "It is very addressable as a CLIA lab," says Anderson, because samples in any case would be collected in the doctor's office and sent off to a commercial lab. The low volume of testing also argues against a kit, and the customer base is diffuse: basically, only Quest and **Laboratory Corp. of America Holdings** would generate numbers.

> **"We have beat our deal expectations and are really optimistic about being able to further accelerate Afirma in 2013."**
> **– Alicia Secor, Genzyme**

The parties consummated the transaction in late January 2012 and held a sales meeting in early March, so the effective launch for Genzyme didn't start until the second quarter. "Without going into specific metrics or revenues or growth rates, I can tell you that we have beat our deal expectations and are really optimistic about being able to further accelerate Afirma in 2013," Secor says. Between them, Veracyte and Genzyme have approximately 30 commercial employees out calling on and working with physicians.

According to Secor, many community endocrinologists have embraced the sample collection and trafficking process, and importantly, have accepted TCP immediately as a convenient one-stop shop. Having a group of pathologists who read cytology related only to thyroid nodules – an expertise that may not be found in the cytology department of a community hospital or a commercial lab – is "a real value-added that has helped increase adoption at the community level," she says. That said, a debate is looming over whether the sensitivity of the test seen in Veracyte's clinical trial will hold up in real-world practice. (*See sidebar, "Data Debate."*)

NEXT STOP: LUNG

Having established the ability to devise and clinically validate Afirma, Veracyte is confident it can pursue development of molecular tests that resolve ambiguous cytology results for diseases of other organs. "It opens up the aperture," says Cohen. "You can go pretty much any place where you can get a small sample."

Devising a test that would avoid costly unnecessary lung surgery is next on Veracyte's list. Veracyte did a lot of work in lung early on, including seeking ways to better determine the cancer risk of patients who have suspicious spots on their lungs after screening with a CT scan. But although the indication and clinical question obviously met the criteria of an unmet need, the company concluded that the risk was much higher than thyroid. In lung cancer screening, for example, if a physician has a bronchoscopy sample taken that yields a benign result, the pulmonologist many times will assume that a nodule was missed – that sampling error could drive a result to be benign. And in lung cancer, missing a cancer has a much higher consequence than thyroid, a more indolent cancer in most cases. "The clinical risk was going to be a challenge," says Anderson. "As a new company, we wanted to bring the first product to market that had the greatest likelihood of success."

Sampling error is also a more formidable issue in lung disease diagnosis. In thyroid, acquiring a testable sample of tissue prior to surgery is relatively straightforward. But the lung is mostly air and it's not so easy to hit the target with a fine needle.

A bronchoscope can't easily get to a third of the nodules people have in their lungs. In interstitial lung diseases, physicians generally don't bother with bronchoscopy to get a small biopsy – the guidelines recommend taking patients straight to surgery to make a diagnosis. The situation is worse in lung cancer,

DATA DEBATE

The imprecision of cytology is an opportunity for **Veracyte Inc.**, but until sufficient real-world experience backs up the data from its validation trial of its Afirma thyroid test, that imprecision could prove to be a double-edged sword. As with any test predicated on cytology, a statistical analysis of sensitivity and specificity of *Afirma* will depend on the accuracy and nuances of classification of the cytology samples. And that will vary from lab to lab.

The prospective Afirma study reported in *NEJM* in June 2012 was designed to reflect the real world by incorporating enough samples to duplicate the variability of FNA technique, practice patterns, and cytopathology results, Veracyte said in an email to *IN VIVO*. Samples were collected from both academic and community-based centers and were accepted in the form in which they were sent to Veracyte: there were no artificial requirements put on the samples that would render them any different from what a physician would submit for routine clinical use.

> **"The concept of claiming a specific NPV is fundamentally flawed when it comes to [molecular cytology] tests."**
> **– Bryan McIver, MD**

But that doesn't satisfy Bryan McIver, MD, formerly of the **Mayo Clinic College of Medicine** and senior author of a clinical utility study looking at early adopters of Afirma.

McIver presented abstract data from Mayo at the *82nd Annual Meeting of the American Thyroid Association* last fall showing the relationship between pretest malignancy and both negative and positive predictive value. He contends that it is not appropriate for Veracyte to claim a 95% NPV for Afirma.

"The concept of claiming a specific NPV is fundamentally flawed when it comes to these tests," McIver says, because the NPV depends on the pretest probability of malignancy, which varies with the cytology criteria used to classify the lesion. For example, Mayo has a much different pretest probability of malignancy of thyroid nodules than Yale for that reason, he says. McIver calculates that the 95% NPV is only valid if the cytology has a known 23% or lower risk of malignancy.

"The concept of avoiding unnecessary surgery by better identifying a truly benign set of nodules is appropriate," McIver says. "There's nothing fundamentally wrong with the science. The problem is in the marketing of it." That is, fostering an assumption that Afirma should perform at a 95% NPV for any sample tested – and using as support the NCCN guidelines recommending that molecular testing be considered if it predicts a risk of malignancy of 5% or less.

But **Brigham and Women's Hospital**'s Erik Alexander, MD, first author of the *NEJM* study, points out that if anything, the trial was very conservative in its numbers, including its estimate of the prevalence of malignancy in indeterminate samples (32%). "I think you'll find in most places it's 24% and if you apply that malignancy prevalence to our specificity and sensitivity, you get an even higher NPV," he says.

The NPV reported in *NEJM* was 95% for aspirates classified as AUS (atypia of undetermined significance) and 94% for those classified as follicular neoplasms or lesions suspicious for follicular neoplasm. "That is reasonably comparable to a benign fine needle aspiration result – cytology," says Alexander. Plus, the data included a half-dozen false-negatives he attributes to the needle not taking up any sample, which lowered the NPV.

According to Veracyte, further studies are under way to continue to evaluate patient outcomes following a benign Afirma classifier result. While those results will take time to ripen, to date, "all indicators are that the test is having the desired impact – which is helping patients to avoid unnecessary surgeries that otherwise would have likely occurred due to indeterminate cytopathology results," the company says. "This speaks to our overall intent to bring more certainty to the practice of cytopathology."

Veracyte can also point to the cost-effectiveness of Afirma, as evidenced by a study from a research team at **Johns Hopkins University School of Medicine**, published in the *Journal of Endocrinology and Metabolism* in November 2011 (before Afirma's launch). Using theoretical estimates predicated on literature review, US government data, Medicare reimbursement schedules, and expert opinion, the review showed the molecular test would result in 74% fewer surgeries for benign nodules without increasing the number of untreated cancers and five-year mean discounted cost savings of over $1,400 with a modest increase in quality-adjusted life years.

McIver may well be correct, and says he has submitted a review article making the case. But ironically, his data from Mayo and potentially other single-site retrospective analyses are a lower level of evidence than what Veracyte has obtained.

where roughly 60% of patients are not even operable, making it impossible to use tissue to refine the diagnosis and direct chemotherapy, says Lanman.

That said, it may not be necessary to hit a lung nodule or involved piece of tissue directly to develop a molecular test. That's because of a possible biological "field effect" in lung disease whereby cells in the neighborhood of a nodule are also affected.

If an injury occurs to some region of the lung that predisposes it to the disease to be diagnosed, not all cells will show the effects at the same time. So a molecular readout may pick up altered gene expression in cells even before they exhibit changes that can be seen under a microscope. If that's the case, tissue from a region of the lung nearby the problem would be instructive. "There is certainly literature that suggests there is a field effect [in lung]," says Cohen. "But if you are thinking with your commercial hat on, you also have to ask, 'Is the fidelity of that instruction good enough to change clinical practice?'"

In terms of sample acquisition, Anderson says it's possible to get around these issues of sampling error in lung, but she won't be specific. "There are ways you can get access to [surrounding tissue] outside the patient," Anderson says. "You can get clever in how you set up a study with the right center where you can actually answer that question outside the normal course of how you are collecting and accruing patients into your study."

Veracyte also thought the marketing and addressability of the lung cancer market was higher risk than thyroid because in lung, when a patient is found to have a suspicion for cancer, a pulmonologist, an interventional radiologist, an oncologist, and a pathologist all will weigh in as a multidisciplinary team. "It would be harder to serve that kind of customer," says Anderson, as compared with targeting an endocrinologist, who basically takes care of a patient from thyroid nodule through diagnosis – and if the patient has cancer, even through treatment. "Reaching and serving the market was a very different proposition," she says. "That elevated thyroid."

With the Afirma launch behind it, Veracyte is more inclined to tackle a riskier program, given the upside of the market. "We are looking at lung cancer and have also broadened that to other interstitial lung diseases," says Anderson, including pulmonary fibrosis.

Interstitial lung diseases are a collection of different diseases that have in common progressive scarring in the lungs. In many cases, high-resolution CT scans are used to make a diagnosis. But a radiologist can only see macroscopic changes, says Lanman. "That standard may only be able to identify people with ILDs late in the game," he says. Even with the best pulmonary pathologists reading a slide, some of the microscopic pathologies are so similar that a multidisciplinary team approach is needed.

Veracyte has said it is in the biomarker discovery phase for ILDs, eyeing a 2015 test launch, but has not disclosed a specific indication nor what the clinical readout of a test would be.

ADDITIONAL PHARMA PARTNERING POSSIBILITIES

The whole genome discovery approach Veracyte adopted could also lead to identification of new drug targets or further diagnostic targets. "Perhaps there's a pattern to better allow us to understand which thyroid cancers are not likely to recur, which would mean we wouldn't need to use radioactive iodine" as treatment, Brigham's Erik Alexander says, adding that he has been in early discussions with Veracyte about that. "I think there's a wealth of knowledge here."

Bonnie Anderson agrees that Veracyte's approach to test development opens up partnering opportunities with a pharma company. "When you are really early in an indication, a therapeutic company will be focused on getting samples on patients with the disease so they can identify targets for drugs," she says. That means also getting samples from patients suspected of having the disease, but who don't.

In lung disease, for example, on first presentation a patient may have one of more than a dozen different clinical conditions. Those same unresolved patients will present in the marketplace when either a test or a drug is available. "When you're identifying patients to enroll in a study up front, you have to have patients with the disease and those representing all of the other diseases it could be if it's not the one of interest," she says. "As a diagnostic company, in the front end of our programs we are looking for the same thing, because we can only develop a classifier on the diagnosis of interest if we know we can differentiate it from all the other things it could be."

The rich genomic data Veracyte collects on samples during biomarker discovery can be used for both the identification of drug targets as well as the development of diagnostic tests. "There are points of commonality there that can be leveraged, which don't necessarily mean you are going down a path of developing companion diagnostics," says Anderson.

Genzyme may well be interested in such a relationship in thyroid, building on the Afirma marketing deal. "Something not covered in the contract would certainly be something both parties would want to explore, given how well things are going," Secor says.

Veracyte will no doubt consider building these kinds of relationships as the company decides whether to become more vertically integrated. "In the next 12 to 18 months we could take a harder look at deeper vertical expansion of the business, or how horizontal we may be with the number of indications to which we plan to expand more fully," Anderson says. The company may go deeper in endocrinology, leveraging its network of thought leaders, collaborators, and community-based practices. "There is a lot of benefit to looking at endocrinology as a deeper growth strategy," she says, "but it would take time."

Moving vertically in thyroid, perhaps deepening its relationship with Genzyme along the way, or going beyond that niche market into a broader indication like lung, would further establish Veracyte's bona fides, making it a more attractive candidate for an IPO or acquisition. "It's a jewel of a company," says Leon. "The challenge is to get a pipeline."

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