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tracking the future of pharmacogenomics

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in this issue

Why Aren't MDs Employing PGx Yet? New Study Aims at Finding Answers

HOW WELL do physicians understand pharmacogenomics? And what is the likelihood that physicians will use these technologies in their clinical practice?

A small team of researchers in the United Kingdom will soon set out to learn the answers to these questions. The current state of pharmacogenomics education at medical schools in the United States and Europe, and thus the use of pharmacogenomics technologies among physicians, means the team will have its work cut out for it.

"My concern is that there is a significant lack of knowledge in the physician community in [pharmacogenomics]," Gary Peltz, head of genetics and genomics at Roche Bioscience, said recently, echoing drug makers' and tool vendors' concerns that their innovations may rot on the vine. "My impression is that it's not a large part of the medical curriculum." [see 5/9/03 *SNPtech Reporter*]

Graham Lewis, a researcher from the sciences and technology unit at the University of York, hopes to find out why big pharma types like Peltz feel this way — and what can be done to turn the tide. "What we're interested in is the pathways between the laboratories and the clinic. This pathway is not straightforward … [but] it does seem to be at a turning point right now."

Beginning in January, the researchers will embark on a 30-month, £150,000 (approximately $177,000) study to look at how these technologies are used in oncology, cardiovascular disease, psychiatric disease, and continued on page 6

In New Hurdle for Roche Dx, FDA Will Need To Approve Each of AmpliChip's Two Markers

ROCHE DIAGNOSTICS' AmpliChip CYP450 microarray will have to overcome several regulatory obstacles before it can gain market approval from the US Food and Drug Administration: The product must be approved as an *in vitro* diagnostic device — not as an analyte-specific reagent, as Roche had originally hoped — and data for each test the product performs must first be OK'd by the FDA, according to an agency official.

The news that each test performed by the AmpliChip must be separately approved by the FDA — the P450 currently tests for the presence of two mutations, and Roche has said it plans to release five additional products based on the Affymetrix GeneChip — comes two weeks after the agency told the firm it may not sell the product in the United States as an ASR [see 11/6/03 *SNPtech Reporter*].

When it was introduced in June, the AmpliChip was heralded by continued on page 7

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PGx Consumers ...

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asthma. "These areas are exemplars, where the development of pharmacogenomics is active and also will bring particular benefits."

Though the researchers must still flesh out the details of their project, they plan to examine not only what kinds of technologies physicians may use — from genotyping platforms to analyte-specific reagents and existing *in vitro* diagnostics — to the regulatory and reimbursement issues that await them. "Obviously, there's a whole range of issues here," said Lewis.

One issue in particular that is causing some anxiety among drug and diagnostic makers is the notion that very few physicians know enough to prescribe even the handful of pharmacogenomics-based procedures, such as ASRs and IVDs, available to them today. "There's a number of pharmacogenomics tests already available; these are not used that much," said Lewis. "There's a number of issues around physician acceptance" of these tests, he said. "'Why don't clinicians use the pharmacogenomic tests that are available at present? What factors and influences allow you to use them in the future as more become available?'" One aim of Lewis' study is to answer these questions.

The project follows research the group conducted that studied the clinical and commercial development of pharmacogenomics. "One of the findings that became clear to us [during this trial] is this whole area about what it would take to … incorporate these technologies into health-delivery systems, which means into the clinic."

The study also comes on the heels of two regulatory watersheds in the United States and in Europe: The US Food and Drug Administration earlier this month issued its much-awaited draft guidance on the use and submission of pharmacogenomics data in pre-clinical and clinical trials [see 11/6/03 *SNPtech Reporter*]; and Britain's Department of Health in June issued a white paper outlining the role of genetics in health-services delivery, which many in industry viewed as an important step in helping define the government's take on pharmacogenomics [view the white paper here: *http://www.doh.gov.uk/genetics/whitepaper.htm*].

Lewis said he has also noticed a "general expansion of knowledge about [pharmacogenomics]," and the number of industry-based clinical trials underway. But regulatory green lights and private-sector investment may not be enough by themselves: Consumers — in this case, physicians — must also be up to speed for the discipline to take off.

Not all the news is bad on the ignorant-physician front, however. In fact, not all medical schools, and thus not all medical doctors, are in the dark about pharmacogenomics. The University of California system, for example, has been aggressively incorporating pharmacogenomics into its medical school and pharmacy school curricula.

At UC San Diego, for instance, school administrators are betting nearly $8 million in state and matching federal funds that students from their medical school and nascent pharmacy school will not only need to learn about SNPs, haplotypes, and gene expression, and how they relate to phenotypes, but that they will ultimately need to use this knowledge together as caregivers [see 10/30/03 *SNPtech Reporter*].

An hour to the north, at UCLA, officials have created a pharmacogenomics research group to study genetic components linked to disorders affecting Mexican-Americans. There, the program recently received a modest NIH grant to study the pharmacogenetics of depression in this population.

More recently, UC San Francisco established a program to build knowledge of pharmacogenomics among in its pharmacy school students. Though the program itself remains modest — it currently supports 45 students — it has caught the attention of at least two big pharmaceutical companies eager for more pharmacogenomics-literate graduates to enter the workforce.

The medical school of the University of Vermont, not known for genomics, has also retooled its curriculum from the ground up recently and now offers a genetics track that runs through all four years of its MD program. (It doesn't hurt that Alan Guttmacher, deputy director of the National Human Genome Research Institute, was the school's director for genetics for a time.)

For his part, Lewis said he intends to speak with tool vendors, such as Illumina and Affymetrix, and pharmacogenomics-technology consumers like Roche Diagnostics and GlaxoSmithKline. "We already have some contact with industry, but obviously we'll be building those contacts," he said. Lewis said that topics for discussion with private-sector players are still evolving.

At a later date, he said, his group may develop solutions — "policy prescriptions" — once the original study is over. The Economic and Social Research Council, a UK-based non-governmental organization that is the main funding body in Britain for economic and social research, will pay for Lewis' research. Most of the ESRC's £78-million annual budget is funded through the British government's Office of Science and Technology, according to the group's web site. Lewis' study, which is one of three genomics-related research projects, is funded by the ESRC's Science in

Society program [view the ESRC web site here: *http://sbs-xnet.sbs.ox.ac.uk/scisoc/*].

"This is a great interest to us, and it is something that needs to receive greater publicity," said Jay Flatley, CEO of Illumina. "I think what [Lewis will] find is, in general, physicians know little today — if anything — about pharmacogenetics or pharmacogenomics and how to apply it."

"The reason for this is that genomics tests have not been available very long, and anybody who has been a practicing physician would have graduated from school long before any of those tests were available, or before any of the [existing] pharmacogenomics capabilities existed," he said.

Flatley said Illumina and Lewis have no formal relationship, but he is willing to participate in the study.

— KL

AmpliChip ...

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Roche as "an important milestone in Roche's development of the individualized medicine market." Roche continues to be optimistic. Greg Heath, the company's senior vice president for clinical genomics, said the device and the test-approval hurdles "do not change much for us."

Specifically, Heath said the company is moving in the direction of seeking FDA 510(k) approval for the device as an *in vitro* diagnostic in the United States, as well as seeking European approval to market the device. "It's a long-term approach," Heath told *BioArray News*, *SNPtech Reporter*'s sister publication. "It is just not the case that you can launch a whole bunch of ASRs and be there tomorrow.

"Once launched, I can't think of any substitute technologies on the horizon," he added. "What we are trying to do is worth doing. This is not going to be easy, there are challenges everywhere we turn."

However, some experts believe that, judging from the letter sent to Roche earlier this month forbidding the sale of the AmpliChip as an ASR, it appears that the FDA would encourage reviewing the product as a *de novo* 510(k) [view the letter here: *http://www.fda.gov/cdrh/oivd/amplichip.html*].

"I don't know the full pathway the FDA would embark upon other than their draft molecular diagnostics guidance," said Ron Eisenwinter, an IVD specialist at consulting firm Boston Healthcare Associates-Expertech, referring to the steps the agency would likely take in reviewing the AmpliChip [see 5/23/03 *SNPtech Reporter*]. "This [draft document] would probably be the one to follow until the ASR regulations supposedly are to be rewritten."

Today, microarray-based diagnostics can fit into one of three submission categories — pre-market approval, a 510(k), or a *de novo* 510(k). The pre-market approval, or PMA, process attracts the highest level of regulatory scrutiny because the products it covers traditionally are life-sustaining devices like heart valves; a 510(k) is a less-stringent application for a device that is equivalent to an existing product and that is not a critical device, like a diagnostic test; and a *de novo* 510(k) is a new category for devices that do not have a marketed equivalent and that do not deserve the rigorous PMA regulatory requirements.

More specifically, the *de novo* 510(k) arises when a 510(k) is deemed "not substantially equivalent" to existing products — which may be the AmpliChip's fate considering it has no predecessor. At that point, the sponsor petitions the *de novo* process to reclassify the device. "Basically, a *de novo* 510(k) device is a PMA-status device dropped down to the 510(k) level," Eisenwinter told *SNPtech Reporter*. "There's fewer hurdles than a PMA, but it's hard to say what the requirements are" for the *de novo* 510(k) "probably because there are no substantially equivalent devices for this." Eisenwinter added that "the rigors would be for the standard *in vitro* diagnostic 510(k)."

Eisenwinter said it is impossible to know how long the FDA takes to review and clear a *de novo* 510(k) application because the agency is believed to have approved just one. However, the process for petitioning a 510(k) as a *de novo* 510(k) may take around eight months — which would mean that Roche may likely begin selling the AmpliChip as an IVD as early as July 2004 if the product and the two tests it contains are approved.

The AmpliChip CYP450 was launched on June 25 as the first microarray-based device targeting clinical applications. The product is designed to probe for polymorphisms in the CYP2D6 and CYP2C19 genes, two genotyping tests that will each have to earn FDA affirmation. According to Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, Roche must obtain agency approval for each of these two tests before the AmpliChip has a shot at the IVD market.

The product will test for the 2D6 gene, which plays an important role in the metabolism of many psychiatric drugs, and for the 2C9 gene, which plays a role in the metabolism of Warfarin, the fourth most prescribed cardiovascular agent, but one with a complex dose-response relationship. Both genes have amassed a body of scientific study.

— MOK and KL