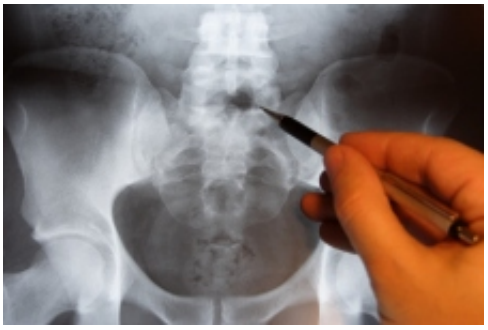
Cancer screening simplified

October 11 2010



Current cervical cancer screening is time consuming and expensive, but now new breakthrough technology developed by European researchers should allow large-range screening by non-medical personnel with almost immediate results and at a much lower cost.

Current molecular assays are cumbersome, expensive and time-consuming and require highly trained technicians. New breakthrough technology tackles all these drawbacks and promises to deliver molecular diagnostics to the GP's office and beyond.

The new technology was developed by the EU-funded MicroActive project, and used state-of-the-art micro-fabrication and micro-fluidic technology to create to desktop 'laboratories'. These offer all the advantages of traditional molecular analysis with none of the disadvantages. It promises a revolution in diagnostic instrumentation.

For the project, MicroActive focused on cervical cancer, caused by specific strains of the human papillomavirus virus (HPV). “It was a good test in that you have a symptom, it could be caused by one of seven different viruses, or even two of them, and you want to know which ones. So it is really a typical case where you have a symptom and you have different possible causes identified by different markers,” explains Liv Furuberg, researcher with SINTEF and coordinator of MicroActive.

There are over 100 strains of HPV, and the human immune system effectively deals with 97 percent of them. The other 3 percent are deadly. Knowing a patient carries HPV is not particularly helpful. Doctors must know the specific strain and whether the virus is active.

Enter MicroActive’s new laboratories, each of which is about the size of a desktop PC. Crucially, this technology reduces a process that typically takes 20 manual steps in a traditional lab down to just two, and as such it can be carried out by anybody who receives some basic training. Unlike lab-based diagnostics, it does not require expert personnel.

There are many possible methods for molecular diagnostics, such as polymerase chain reaction amplification, or immunoassays. But in some cases, these methods can lead to false positives. MicroActive chose to focus instead on messenger Ribo-Nucleic Acid (mRNA) as a marker for an active virus.

Genes get expressive

In gene expression, typically mRNA is transcribed from the DNA template and then carries that ‘message’ to the ribosome where a protein is then synthesised, or created, from the mRNA in a process called translation.

But mRNA coding for specific proteins, known as E6/E7 proteins,

reduces the production of other proteins that regulate the cell cycle, which are important tumour suppressors. Their presence dictates the likelihood of cervical cancer development down the line.

By contrast, the current dominant testing technology for cervical cancer is cell-based tests. These tests return false positives at a rate between 50 and 75 percent. A false positive indicates the presence of the cancer causing virus where in fact it is not present.

These false positives are not only time-consuming and resource wasting, they also cause enormous stress to people who get false results. By testing for specific protein-coding mRNAs, MicroActive avoids the risk of false positives.

The test itself is extremely simple. A cervical smear sample is taken in the usual manner and the sample is added to a mixing agent in a syringe and the syringe is then added to the first 'laboratory' in the process. Here the sample is extracted from the syringe, prepared and applied to a disposable micro-fluidic chip.

mRNA detective

Micro-fluidics is the branch of nanotechnology that develops methods to transport liquids at very small scales and nanoliter volumes. Once the sample is prepared, the chip can be transferred to the detection module.

The first step in the detection process is Nucleic Acid Sequence Based Amplification (NASBA), used to create a large number of markers. Next biomarkers – lab-developed molecules that only bind to specific nucleic acid strands – are introduced.

"In our tests we looked at just two different markers, because it was [enough] to prove the concept," stresses Furuberg, "But there are eight

channels in our disposable chip, and each channel can test for two viruses at a time, so we could test for up to 16 different markers."

"What's more, this system is more sensitive than traditional tests," reveals Furuberg. "Normally, when you miniaturise something, sensitivity will always be a problem, because you have a much smaller sample, but you still need to detect your markers. So typically miniaturising something means you need to increase the sensitivity."

Biggest challenge

But, Furuberg asserts, lab-based microassays typically amplify a group of markers at the same time in the same sample. "But in MicroActive, we separated the markers between different droplets of the sample. So the system restricts the number of markers to just two per channel and you have a much greater sensitivity."

The biggest challenge facing the project, however, was preparing the sample. Typically, this is a very elaborate process – preparing the cervical smears, extracting the mRNA in a way that is good enough for further amplification, in other words getting a clean sample. Cervical smears are complicated samples, so getting a sufficiently high quality sample for amplification is difficult.

"We studied every aspect of the process in detail, even before the cervical smear sample is taken, to try and develop the cleanest approach possible, and it was a series of refinements that allowed us to achieve the level of quality required. For example, the choice of sample filters that were very important for the process," Furuberg explains.

The team's dedication paid off when they tested the system with known HPV-carrying samples at the end of the project. And in tests against the current gold standards for HPV detection, the MicroActive system

performed very well, either matching or exceeding the current state of the art.

MicroActive defined a new state of the art of molecular diagnostics for cervical cancer. But that is just the beginning of what they could achieve. The Norwegian company NorChip seeks to commercialise the diagnostic platform.

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