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Big picture, big rewards—how to think about digital

By Ajit Singh, PhD

Ajit Singh, PhD, chief executive officer of BioImagene, spoke in June at the CAP Foundation's Futurescape conference in Rosemont, Ill. The title of his talk: Digital Pathology—The Last Missing Link in Personalized Medicine. An abridged version of his presentation follows. Before becoming CEO of BioImagene in 2008, Dr. Singh spent 20 years at Siemens in various areas, among them radiation oncology and digital radiology.

What did digitization transform in radiology? If you look at x-ray circa 1900, the CT a few decades years later, and the ability to read a CT like 2D slices—these developments were clearly important. However, the ability to take the nascent three-dimensional data and run CAD algorithms was truly significant. Here's a great example: 31,567 asymptomatic people at risk for lung cancer underwent a low-dose CT. CAD algorithms were run, and 484 people were identified with stage one lung cancer (N Engl J Med. 2006;355:1763–1771). That's the power of screening. This would never have been possible in the nondigital world.

Fifteen years of digitization of radiology can be summed up as follows: Productivity went up by about 20 percent, report turnaround time went from three days to three hours, past radiology studies became more available—up from 60 percent to nearly 100 percent, handling errors went down, clinician viewing factor went up by a factor of two, comparison with prior studies went up by a factor of five, screening of the breast, lung, and colon went up by a factor of 10.

But that's not all. One could now do things simply not feasible in the pre-digital world. For instance: 3D visualization, quantitative analysis, fusion of anatomy and physiology like PET CT, fusion of MR functional image and MR morphological image, contextual access to the anatomy at-lases at the point of care, contextual access to similar cases at the point of care. And the list goes on.

The first simply automated an existing standard of care, and the second set redefined the standard of care. Digital pathology is bound to do both.

I remember my first assignment in about the late '80s, early '90s. The first hospital to go filmless worldwide was a hospital called SMZ in Vienna. Professor Walter Hruby at SMZ took the entire hospital by a dictum of mandate from film to filmless. Not a single

department, not a modality. Lock, stock, and barrel, everything went filmless in radiology.

When we were negotiating with them, we asked, 'Why would you like to buy a PACS?' 'Well, it'll save us film cost,' they said. We asked, 'Well, what if your film vendor cuts the cost of film by half every year?' Which it did. 'It won't save you money.' We were doing reverse psychology with them. 'Why then would you buy a PACS?'

They said, 'Well, we might save on head count.' I said, 'In Austria you'll actually fire people? Are you kidding me? But let's assume for a min-ute you were allowed to do that. How many people would you get rid of?' 'Twenty,' they said. 'What kind of people are they?' I asked. 'They're file runners, film runners.' 'How much do they earn per year?' 'Well, the equivalent of maybe \$25,000 to \$30,000 a year.'

We said, 'When you have a PACS you will need a system administrator. You'll need a database manager. For over \$100,000 per person, most of that savings goes away. No reason to buy a PACS. What's next?'

'When they check out the radiology film, they never bring it back, and 30 percent to 40 percent of the time, the film is lost,' they said. 'A film misfiled is a film lost, like in a library.'

We said, 'Here's what you should do: Each time somebody checks out a film, they bring a 20-schilling bill, they pin it to a corkboard, and sign their name. When they bring the film back, they take their 20-schilling bill back.' They did this, and what happened? The lost film rate went from 40 percent to five percent. Twenty schillings was sufficient for them to bring a film back. So lost film was not a good enough reason to buy a PACS. 'Next?'

'When we do these studies,' they said, 'sometimes we have to compare with old data, and when we fetch old film—.' I said, 'Ah, now that's interesting. How often do you fetch old film?' 'About 10 percent of the time,' they said. So, we went there and did calculations: We need that much space, this much bandwidth, and so on. We pulled together a PACS.

After one year of implementation, how often did the old study get retrieved? One hundred percent of the time. That was redefining a standard of care. At many places it is now malpractice if in the digital world you have a case and you do not retrieve a prior study for a comparison or dis-ease progression.

One has to think in those terms. The conventional things—saving on the storage of slides, saving the FedEx bill, getting additional reimbursement—are all good. In the short run, you do need to harness these savings. But in the long run, think of the big picture. Then think of redefining the standard of care.

What can digitization do in pathology? Here are the things you could not do before: quantitative comparison, case sharing and collaboration, image analysis, remote frozen sections, data mining for decision support, and personalized medicine. And here are the things that can be done at lower cost and with greater efficiency: archiving and retrieval, tumor boards, remote case review. In addition, primary diagnosis is more efficient, there are fewer handling errors, and slides are more readily available.

In other words, whatever we said for radiology will happen in pathology. While I've been extolling the virtues of copying and pasting from radiology, there are also differences.

There are things that are analogous; we just talked about them. But there are also things that are complementary—image-guided biopsy for instance.

But probably the most important dimension is convergence. The two modalities will converge technically and clinically. It's only a matter of time, and I encourage you to be in the driver's seat as opposed to watch it happen.

To make all of this happen, you need technology. First you need scanners, and a scanner, in my view, is the necessary evil of being in this business. It will always get commoditized. Whether we have line scanning or tile scanning, or one minute per scan or 30 seconds per scan, 160 slides or 120 slides—all of that eventually evens out. 'Eventually' is sometimes three months away, sometimes six months away—not a lot of the time.

Then there is workflow software—more difficult and important. Finally, most important are companion algorithms, which are used to do a quantitative assessment to determine suitability of specific therapies for the specific patient. I believe the diagnosis is fundamental. It is center stage. We should be thinking of companion therapeutics downstream and companion algorithms upstream. Stated differently, for every targeted therapy, there's a companion diagnostic. For every companion diagnostic, there's a companion algorithm.

Think of the magnetic resonance imaging world. When functional MRI came out and choline citrate ratios were applied to prostate, there was nothing visual to look at. It was multidimensional data. And by presenting it in a two-dimensional image, you ruin the inherent richness of the data. You ought to be doing image analysis or data analysis in two-, three-, or four-dimensional data to sift out the one thing that matters: diagnostic confidence.

Scanners—you need low-end, mid-end, high-end, bright-field fluorescence. Most people who purport to be in this business would have it. Aperio has it, BioImagene has it, Omnyx will have it, and so will all the others. Eventually it will become a commodity. The software has to do the end-to-end workflow coordination. The software has to be an orchestrator.

Some might think that if you have a scanner and software, you have digital pathology and you're done. Not so. That can be some company's advertisement, but that's not digital pathology. We've got to be looking in terms of clinical use cases. And that's where I believe the upper layer of companion algorithms becomes relevant.

If personalization in medicine has a chance, and pathology is to be an enabler, companion algorithms are going to be the key driver. Take image analysis for H&E. Epithelial recognition, nuclear morphometric analysis, mitosis detection, gland detection. You can have SBR [Scarff-Bloom-Richardson] scoring for breast cancer, Gleason scoring for prostate.

Now, let's move to IHC. Think of HER2/neu IHC, a membrane algorithm, a nuclear algorithm, a cytoplasmic algorithm, scoring of HER2 FISH, CISH, prostate, a triple-stain IHC. What I'm trying to portray is that a vast repertoire of algorithms is going to be key: p67 for prostate, HER2 for breast cancer, EGFR testing for colon and lung. Not all are FDA cleared, but we are working with multiple clinical sites to perform validation. And the same is true for gastrointestinal stromal tumors, oligodendrogliomas, and lymphomas and leukemias.

Investing in a platform technology from which you can crank out an algorithm each week is what's needed. And I say this with some experience. In radiology, getting CAD to work was a very long shot. Not because the technology was hard. It was, but then the clearance from the Food and Drug Administration was harder. It invariably turned out to be a PMA; there was no predicate device.

Companion algorithms will enable companion diagnostics. Hence, they will enable personalized medicine. The key knowledge, or key enabler, is what I call 'emergent knowledge.' Hierarchical knowledge will never work here. It has to be emergent knowledge whereby you harness the collective intelligence of a community to pull knowledge to the point of care.

To implement this, you collect large databases of patient data and external medical knowledge. You then mine the data and create personalized knowledge models. Then you apply that knowledge model to the point of care in the clinical workflow. You have various sources of data on the left: Radiology images, lab pharmacy text notes, proteomics and genomics, and pathology images. You need to extract symbolic information from the data, and then recombine it taking all conflicting evidence into account. Mathematically, it's a very difficult problem.

However, if you do it right, you create a knowledge model for the disease state, or for the diagnostic, that you can update every time you have a new patient. And then you apply the model at the point of care.

The problem is, anatomic pathology is not digitized—yet. If I'm looking at oncology, where one-half of the diagnostic information or more is coming from pathology, and it's all analog, what do you mine?

If I say, 'Digital pathology is that last missing link,' it is not an exaggerated statement. It is that last missing link. A lot of mathematics for downstream work is available. Radiology is digital. Clinical pathology is digital. Genomics was born digital. Proteomics, to the extent it's there, was born digital. Anatomic pathology is almost 100 percent analog.

As we know, with the discovery of new biomarkers, the role of quantification will increase. Companion algorithms will redefine standards of care. For all of that to happen, knowledge has to be disseminated very fast. Hence, Web 2.0 will play an important role. Consider Path-Xchange. This is not BioImagene's platform. We are a platinum sponsor of Path-Xchange, but it is a vendor-neutral platform. It is led and run by a third party. Visitors can browse the case gallery, browse cases in a category, browse a case, look at that case with a digital viewer, and browse similar cases, upload new cases, and so on.

Image-based search is possible today. You can create a case, scan slides and upload, digitize slides by mail, create your own case gallery, search for users and cases, search only pathology sites, do professional networking, read pathology blog feeds. There are 1,000 pathologists live on this site just in the past two months. How many anatomic pathologists are in the world? Twenty-five thousand. Four percent of them went live in two months. So I do believe there's a trend in the making.

The tight collaboration with your brethren in radiology and elsewhere in molecular diagnostics is going to be essential. The fragmentation we have long had is totally artificial. A disease state doesn't understand that it's being looked at by radiology or anatomic pathology or molecular methods. So, I do believe that digital pathology will automate standards of care and redefine standards of care. And it will serve as the last missing link in personalized medicine. Digital pathology has been in a beginning state for some time. It is the end of the beginning; the time for adoption starts now.