

Editorial

Twenty (forward looking) questions

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The old proverb about the sudden appearance of the teacher when the student is ready to learn has been a good guide for our roles as both learners and teachers. Select business schools have long recognized this truth about motivated learners and hence have given admissions preference to students with enough “real-life” experience in the business world to know the “questions” that they don’t know the answers for. For pathologists it is not uncommon to come away from a course with a few “ahha!” moments of recognition regarding that puzzling case they had last week or last month. The day-to-day problem solving nature of our work brings us an unending supply of stumper cases and problems to motivate lifelong learning. But sometimes, one needs a wake-up call of sorts to see if there are more questions and answers that might be worth thinking about. This kind of intense dosing of challenging questions to further motivate learners with new questions is also a valid learning technique.

The recent Molecular Medicine Tri-Conference (Tri-Con) held in San Francisco, February 10-13, like its two decades worth of precursors, provided a snapshot of many new and exciting technologies being used at the research level internationally, and offered a stimulating environment with respect to both kinds of questions, those generated from our own experience and those offered as futuristic challenges. These are the “imagine if” kind of glimpses into the potential landscape of medicine generally and perhaps pathology specifically, that may not be too far off. This yearly meeting provides a base from which technology and research beyond that currently encountered in clinical laboratories can be explored and influenced. As such, it has some exciting and frightening implications for the profession of pathology and the operation of clinical laboratories. From our experiences

in several of the sessions and different tracks at the conference, we started a list of questions that we might want to have answered in the coming years pertinent to the readers of the journal. Twenty possible questions that occurred to us are provided in Table 1, with apologies in advance to any of the presentations and presenters that did not prompt a question on this list.

If we were playing 20 questions with an average focus group of practicing pathologists, these would likely seem to be unanswerable to the average contestant, and may not have even crossed the threshold of consideration. However for someone coming home from the 2014 edition of Tri-Con in February, these are questions that forced their way into consciousness, and some of the answers were quite startling. Granted that some are more important than others, yet they all have the potential to impact what people like us are going to do with our time in the next year to some degree, as well as to a much greater degree in the coming 5-10 years. We have selected two representative questions for each time interval, near future, intermediate future, and longer term and offer a brief discussion of the implications of these questions. There is value in surveying the landscape ahead to see whatever hints on the horizon allow us to adjust our course today. Join us in thinking

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Table 1: Twenty questions from the molecular medicine tri-conference meeting

Why would I need a set of new guidelines for telepathology?

Aside from current paradigms for acquiring WSI images through a conventional scanner-light microscope, are there other means that might offer different trade-offs between focus, field of view and resolution?

What is *in-vivo* microscopy and why should a pathologist care about it?

What if new imaging tools were able to develop measurable criteria for diagnosis? What's going to be used in the next few years?

Given the migration to smaller and smaller samples, what means and paradigms of multiplexed testing are going to win out?

What does a pathologist untethered from the light microscope do? How will I explain it to my grandkids?

What does WSI, genomics and molecular analyses reveal about the weaknesses in our current foundation paradigm of "artifacts"? Is the system going to be totally disrupted by liquid biopsies, or a need for snap frozen fresh tissue?

Are there ways to quantitate mRNA or miRNA using digital microscopy tools?

When we can measure things to new levels of certainty (i.e., down to the single molecule level) what changes in other paradigms?

What if development of an assay, standardization across a platform and deployment across a system (even potentially including low resource settings) were as easy as writing an app for your phone? Or easier?

How far along are diagnostic assist algorithms? What kinds of problems will they be best suited to tackle for us and how will they be vetted?

What are the practical solutions for managing image data in pathology today? Where are the pitfalls in having these reside in the LIS or outside the LIS? What about "complete solutions"? What architectures predict failure versus long-term robustness of utility?

The issue of adoption of digital pathology among diverse interests in a department—what can accelerate or impede progress? How do I best plan for implementation beyond just niche applications?

What if you had an assay system that was totally indifferent (relatively) to specimen type?

When the clinical trials paradigm shifts from organ-based to pathway-based and the specimen drives the trial eligibility, will pathologists be more involved or less and how?

What could you do with a flow-cytometric technique such as the CyTOF instrument that allowed single cellular determination of up to 40 or 100 different parameters each independently labeled by whatever antibody or other chemical tag linked to a lanthanide isotope?

What are the tools now in existence to manage the onslaught of big data that pathologists might hope to utilize to practice better population-predictive and personal-predictive medicine?

What does the value proposition for WSI look like today?

How far off is NGS as a surrogate for other existing current testing?

What am I able to and going to do about any of these questions?

WSI: Whole slide imaging, mRNA: Messenger ribonucleic acid, miRNA: Micro-ribonucleic acid, LIS: Laboratory information system, NGS: Next generation sequencing

through some of the questions where the answers seem most intriguing based on the presentations offered at the sessions we attended.

NEAR TERM

1. Why would I need a set of new guidelines for telepathology? And where will I go to find them when that need arises?

This need may not be that far down the road for more and more pathologists as the options for insourcing of cases and simple and potentially low cost streaming of microscopic images continue to grow and the demands to make pathologists more productive mount. The first set of guidelines was provided by the American Telemedicine Association in the 1990s.^[1] These guidelines have been recently updated to reflect current capabilities and legalities. Dr. Liron Pantanowitz gave attendees a first glimpse into these guidelines in advance of publication later this year.^[2] Together with the Canadian document issued in 2012,^[3] these are certain to be useful to successful incorporation of telepathology and digital pathology (DP) tools into practice.

An interesting corollary to consider in this arena

is the impact that telepathology can have on the next generation of pathologists in training now. Many people believe that telepathology skills ought to become more centrally integrated into core opportunities in residency training experiences. However, what will the impact of this be? While often today's residents are more prone than their mentors to perform stains *ad infinitum* to arrive at a level of diagnostic certainty approaching six sigma, one might similarly pose the query of the impact of (seemingly limitless) real time consultation through telepathology on one's confidence in making a diagnosis. Yet, if we could reduce that predictable 2-5% error rate in frozen section diagnosis alone by making telepathologic consultation universally available, this effort would be beneficial.

2. What is *in-vivo* microscopy and why should a pathologist care about it?

White light bright field microscopy has been around for a very long time. The data underlying its use in diagnostic pathology and patient care is abundant and robust. However, the paradigm is not immune to disruption, as technology and the drive for lower costs and more personalized care change the models of care delivery. The collection of technologies that

fall under the heading of *in-vivo* microscopy has begun to cross the interface from investigational research to clinical applications. As this happens, the discussion of how they will be applied to clinical issues, and who will use and interpret the “microscopic” images acquired using these modalities become profoundly important to pathologists and our patients. The presentations by Drs. Maria Shevchuk and Kamran Badizadegan opened this Pandora’s Box of tools ripe for the enrichment of the pathologists’ armamentarium, or the destruction of their central role in patient diagnosis and care.^[4]

These new tools offer the opportunity for “point of care pathology,” but they also pose the threat of assumption of the critical tissue-diagnosis role by others wielding the endoscope, catheter, or needle bearing the new microscope in the patient encounter. Will pathologists move closer to the patient to use their skills in microanatomy and tissue pathology image interpretation, or remain tethered to the modalities of 19th century tissue processing, embedding and staining and their inherent time-lag, perhaps seeing their pertinence to the decision-making in the clinical encounter diminish or even vanish? Tactically, the work of the College of American Pathologist’s (CAP) *in-vivo* microscopy work group would seem to be to call out awareness of this two-edged sword of opportunity or threat to our colleagues, as they did with these presentations.

A general observation from the list of 20 questions is that in the near term, information technology is sweeping across clinical care in many different ways. Furthermore, it is impressive the number of different directions pathologists will encounter informatics issues in the near-term future. Whether it be electronic health record construction and incorporation, DP implementation, telepathology applications, or the direct challenge of *in-vivo* microscopy to our profession, these are issues that pathologists and our organizations like the CAP need to have well in hand.

INTERMEDIATE TERM

1. Given the migration to smaller and smaller samples, what means and paradigms of multiplexed testing are going to win out?

Many of us regularly evaluate very small tissue samples, such as those obtained at a needle biopsy. More and more clinical scenarios demand more than just the conventional benign versus malignant differentiation of cytological evaluation. With this shifting paradigm of a more explicit and specific diagnosis, along with all the potential prognostic and therapeutic immunohistochemical (IHC) and molecular markers, the issue of sample adequacy is

far from trivial. Enter the world of multiplex testing on the same sample. Of course we have had some exposure to this model of evaluation with multicolor flow cytometry, multi-antibody IHC cocktails and such, but several of the Tri-Con presentations peeled the scales from our eyes to see a whole new level of potential multiplex methods. For example, Dr. Richard Levenson’s presentation on multispectral immunofluorescent methods illuminated the potential for perhaps as many as a hundred antibody-antigen interactions being simultaneously detectable in a tissue sample. Dr. Kenneth Bloom’s discussion of the capabilities of the Multiomyx™ methodology to obtain multiparameter (<http://www.multiomyx.com/> accessed 31 May 2014) phenotypic data on the same cells for up to 60 antigens revealed the integration of digital imaging and advanced IHC techniques, while Dr. David Rimm’s presentation reviewed the value of the quantitative multiparameter methods pioneered in his laboratory.^[5,6]

These topics would have been enough to stretch one’s mental envelope of what is possible. However, the presentation by Dr. Garry Nolan, “Mass Tags and IHC—A New Frontier for 100 Parameters and Above,” on the potential of cellular quantitative multi-parameter data (such as quantitative micro-ribonucleic acid (miRNA) or messenger RNA) that can be obtained using the new tool of lanthanide-linked plasma ionization mass spectrometry literally exploded the cell membranes around what is possible. While this instrumentation will not appear on capital laboratory budgets for yet a long time, the concepts of what might be measurable certainly changes mind sets.^[7]

While some of these are currently available for clinical application, the prescient among us who like Wayne Gretzky want to skate to where the puck (value) is going to be eye these potentially competing technologies with anxious eyes. Just because something is possible to do doesn’t always mean that it will be done on a scale that shifts health care. Costs and benefits (returns) will be measured again and again as they shift over time to determine winners and also-rans. About all we can say right now is that multiplex testing of some sort on cells or tissue is likely to have several sticks competing for time on the ice sheet. Start-up costs (training, validation, and capital equipment) as well as operating costs and performance in the game will be key determinants of who stays and who sits. Pathologists need to fill the roles of trainers, coaches, referees, and athletes in the evaluation of these new tools that will challenge our minds to make meaning from such multidimensional datasets.

2. What does whole slide imaging, genomics, and molecular analyses reveal about the weaknesses in

our current foundation paradigm of “artifacts”? Is the system going to be totally disrupted by liquid biopsies, or a need for snap frozen fresh tissue?

This question haunts many pathologists looking at a career term stretching beyond 5 years into the future. In this arena, Dr. Sandy Borowsky’s presentation on “The Quest for a Universal Fixative: Measuring Fixative-induced Morphologic and Antigenic Variation,” provided some measure of reassurance that the predictive molecular data may well be sufficiently preserved in our longstanding companion, neutral buffered formalin. However, reassurance should probably not lead to slumber on this front.^[8]

Presentations in some of the sessions discussed the significant utility of the “liquid biopsy,” or various circulating biomarkers, evidence of a very active search for new and useful means to monitor and diagnose disease. In the intermediate term, the questions incorporate concepts revolving around nanotechnology, sampling, single-cell analysis, and the development of decision-making algorithms directly leading to diagnostic processes. Clearly, these areas will change the face of the clinical laboratory and provide new and challenging tools to pathologist judgment and decision-making. Today’s pathologists need to take account of these questions and directions sooner than later, and shape the debate, the technologies, and the implementation based on their understanding of disease, workflow, patient and process management and leadership.

LONGER TERM

1. When we can measure things to new levels of certainty (i.e. down to the single molecule level) what changes in other paradigms?

The CyTOF™ <http://www.dvsscience.com/cytof-instrument.php> accessed 31May 2014 instrumentation is just one example of ultra-high assay sensitivity of detection that might impact anatomic pathology samples, but discussion of newly developed clinical laboratory instrumentation also needs to be mentioned as these begin to push downward the detection thresholds for standard and newer analytes such as tumor markers, drugs or infectious agents. It is an easy jump to a different treatment and monitoring scheme for a patient with a chronic viral infection when one’s detection threshold moves lower by several orders of magnitude. Dr. Randall Hayden spent time discussing the role of viral loads and sensitivity in the development of infectious disease testing as just one example of a paradigm shift accompanying this kind of testing change.^[9]

2. What does a pathologist untethered from the light microscope do? How will I explain it to my grandchildren?

In the longer term, we may indeed need to question what we really do as pathologists. Traditionally, we have divided our work into categories which are reflected in our approach to residency training and the certification process of the American Board of Pathology. In all likelihood, we will have to expand our interpretative skills to accommodate a range of new testing approaches as the boundaries between pathology’s core certification disciplines blurs. Furthermore, we will have to aggregate knowledge from multiple specialty areas and become experts in adapting this knowledge to patient centric integrated reporting.

Change is always difficult and it is true that some aspects of microscopy will probably always be inherent to the profession. However, the use of electronic means to consolidate data and diagnostics will challenge the way we do our work and the processes we use to reach a diagnosis. Already we have seen shifts in the use of tissues to include bio-banking and tissue qualification for genomic studies. In many respects, these new activities are the harbingers of our activities as aggregators of source material, data, and diagnostics. Practice models for the next generation pathologist are written in these clues and questions.

The degree of effort currently underway within organized pathology to confront these portentous questions is not trivial. CAP has staked its savings, indeed its future, on being able to manage the changes required in the field to remain relevant. Committees, work groups and project teams exist to promote, facilitate, integrate, advocate and educate on *in-vivo* microscopy, DP, next generation sequencing, and informatics. The United States and Canadian Academy of Pathology (USCAP) likewise has upped the effort around education in these critical areas. The Association of Pathology Informatics (API), Digital Pathology Association (DPA), American Society for Clinical Pathology (ASCP), American Pathology Foundation (APF) and the rest of an alphabet soup of others are likewise not oblivious of the implications of the kinds of questions we have posed here. This is fortuitous, as a moving ship, even a large one such as professional pathology, is much easier to steer when it is moving than at a standstill. Still, steering and maneuvering the course will truly require an all-hands effort.

SUMMARY

Knowing the questions is one thing. However, it may be equally important to be engaged in the dialogue

developing around the questions. Participating in the system design phase, even if not entirely engaged on the conceptual phase, makes for a better product outcome if one is the user or the trouble-shooter at the end of the line. We strongly encourage pathologists to engage with our industry and research colleagues early in the design and conceptual phase to optimize the ultimate outcomes, lest we all be left behind (or out) and find ourselves struggling with tools poorly fitted to our processes and capabilities, if not the pertinent questions.

It is equally important to be engaged with our colleagues within and beyond pathology, and the organizational efforts to manage the change process. This is not strictly self-servingly seeking to co-opt a disruption that would be our demise, provided it is done with the patient's interests above all, but will only be the healthier for an alert and engaged membership—be that in API, CAP or whatever group best reflects one's interests.

Furthermore, finding the teacher when the question is at hand is not always a “given.” We may need to expand the horizons of our educational offerings, and where we look for answers if we are to remain relevant. However, having been challenged by those who are seeking the answers helps when the question is up front and personal – in today's slide folder, next week's consult request on your computer work list, or the simple query of a son or grandchild about what one does all day.

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