Artificial Intelligence - The Third Revolution in Pathology

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Abstract

Histopathology has undergone major changes firstly with the introduction of Immunohistochemistry, and latterly with Genomic Medicine. We argue that a third revolution is underway: Artificial Intelligence (AI). Coming on the back of Digital Pathology (DP), the introduction of AI has the potential to both challenge traditional practice and provide a totally new realm for pathology diagnostics. Hereby we stress the importance of certified pathologists having learned from the experience of previous revolutions and be willing to accept such disruptive technologies, ready to innovate and actively engage in the creation, application and validation of technologies and oversee the safe introduction of AI into diagnostic practice.

Histopathology became an established, global and accepted clinical discipline in the first half of the 20th Century (see figure 1, a chronological representation of the timeframes discussed in this article). Immunohistochemistry (IHC) became a regular component of the pathologist's diagnostic armamentarium during the late eighties and early nineties [1]. Pathology adopted IHC with relatively little effort. After all, IHC shared the same qualitative visual interpretation and subjectivity as histology. At the same time, pathologists were suddenly empowered to understand and interpret the overall expression of proteins within the tissue context. The evaluation of the intensity of the expression, the subcellular localization and the tissue types expressing it provided important information in both diagnostic and discovery. The rate of adoption has been phenomenal, helping the delivery of a more accurate and sophisticated taxonomy of diseases (diagnostic value), and also the performance of key tests with a genetic, prognostic and predictive value [2]. Indeed, it is not surprising that in the era of whole genome sequencing and high-throughput transcriptomics, the preferred companion diagnostic is still not a mutational test, or a gene expression signature assay, but a tissue-based monoclonal antibody, as it is easy to adopt, widely available and reasonably affordable. This almost-universal availability ("the best thing of IHC is that everyone can do it"), however, has not come without criticism ("the worst thing of IHC is that everyone can do it"), perhaps highlighting the need for a more rigorous design, validation and delivery of IHC [3]. In any case, the adoption of IHC became the first main substantial change in the practice of diagnostic pathology: a true revolution.

While the code of the genomic information was discovered in the 1950's [4, 5], we had to wait a few decades [Fig 1] to see the promise of molecular biology and nuclei acid-based assays incorporated into routine tissue diagnostics. This second revolution ("the molecular diagnostic revolution") was different in many ways. For a start, its application was only ¨tangentially¨ related to pure morphology. Indeed, adequate tissue and cellular pathology is *conditio sine qua non* for adequate tissue molecular diagnostics, in terms of good baseline morphological taxonomy and optimal preservation of the nucleic acids. However, from that point onwards, the techniques, the concepts and the interpretation did not require knowledge of the morphology of disease, but rather of the molecular basis of disease. The result is that the true ownership of these tests across the world is very different. In countries like Germany, the molecular interrogation of formalin-fixed and paraffin-embedded (FFPE) material and cytology samples is owned by and large by traditional "Tissue Pathology Laboratories". In other places such as the UK, the plans to establish Genomic Medicine as a separate discipline, often only peripherally includes tissue pathologists. The controversy as to who owns the interpretation of the genomic information in diagnostic/clinical practice has not abated. The answer to this question may hold the key as to how pathology, genetics and laboratory medicine will look in a couple of decades, and the associated allied workforce. Perhaps pathologists are losing a great opportunity by not embracing these technologies upfront and embedding genomics medicine as a compulsory element of tissue pathology training – so allowing pathologist to actively lead this second revolution, rather than simply facilitating it [6, 7].

In our opinion, Artificial Intelligence (AI) represents an incipient "third revolution",that is strongly knocking at the door of pathology with attendant opportunities and challenges. AI represents a range of advanced machine technologies that can derive meaning and understanding from extensive data inputs, in ways that mimic human capabilities in for example, perceiving images. In pathology, this can therefore, take several forms, principal of which is the automated interpretation of pathological images. . AI is underpinned by computer algorithms which interrogate the image pixels and quantitatively map them to predefined classes which represent tissue structures or disease states. The recent revolution in "deep learning" methods utilize the power of convolutional neural networks and massively parallel processing capabilities which today are cheap, to replicate human perception and drive image understanding software. Using AI algorithms, it is becoming possible to precisely and automatically identify tissue patterns which, for years, have been the exclusive domain of pathologists and the human visual cortex [8, 9]. This extends way beyond the quantitative analysis of IHC using image analysis, to the automated analysis of complex Hematoxylin and Eosin (H&E) tissue patterns, which represents the bulk of what pathologists must interpret and where the biggest diagnostic challenges exist. Opportunities will thus be presented to enhance diagnostic practice. Some examples of AI development that will provide such opportunities include:

a) distinction of benign and tumor

b) grading of dysplasia and *in situ* lesions [10]

c) evidence and extent of invasion

d) identification of micrometastases in lymph node resections

e) IHC/ISH scoring of multiple biomarkers and topography of the immune response [11]

f) percentage of tumor and overall cellular content

g) extracting new patterns from the digital images and clinical correlates (next generation morphology)

h) automated management and prioritization of pathology workflow

Along with opportunities though, come challenges. We have to accept that some AI developments may actually result in the automation of certain tasks in pathology, challenging to some, but also seen by others as an opportunity to overcome pathology workforce issues or to improve patient outcomes. When these are safe, reliable and improve the working experience of pathologists however, then we should see these as enablers which can introduce significant efficiencies and cost savings in pathology and provide further opportunity through the freeing up of time to attend to activities such as complex case reporting.

In Figure 2, we illustrate how AI in the future could facilitate three morphological-based activities from scanning the H&E sections from cases subsequent to staining. In such a model, lymph nodes may be screened for micrometastases [12], the evidence and extent of invasion may be determined and the tumor sections would be determined for regions for macrodissection [13], all determined within the first 24 hours of the analytic process.

Of course, the starting point for AI is digital capture of whole slide images using digital pathology (DP), a discipline which itself is growing rapidly in primary diagnostics. The "tissue diagnostic laboratory pathway" (depicted in Figure 3) is today arguably the most fragmented and complex pathway in the field of laboratory medicine. One major opportunity of DP, is in the potential to reduce this fragmentation, streamlining workflow which can be realized through the adoption of DP for routine diagnostic practice. Only then can the true impact of AI be realized. Indeed, the additional performance of AI to DP in improved workflows, diagnostic precision and predictive power may be the ultimate driver for adoption of DP for primary diagnostics. Thus the combination of AI and DP if adequately developed and integrated, adds value to pathology as a discipline and ultimately to our patients. Such efficiency savings and added value of DP is in agreement with the justification call of Flotte & Bell [14]. Moreover, this combination of DP and AI [15 has the potential of transforming the way we operate as diagnosticians and becoming a "third revolution".

In the process, AI will also extend to the complexities and challenges of data integration across the entire spectrum of epidemiological, clinical, radiological, pathological and genomic data that ultimately will chart the course for patient therapy and clinical outcomes. AI has the power to transform our ability to see through this complexity and establish new highly integrated diagnostic signatures which provide an opportunity to merge large data sets and provide insights not possible with the human eye or the human intellect alone. The challenge offered by this facility will be to translate and apply the results to

meaningful, safe and robust predictions to treatment options, and reliable diagnostic and prognostic opinion.

It is not possible to overemphasize the potential impact that this new development could have on medicine in general [16,17], affecting most levels of information management and understanding in medicine through the access to comprehensive clinical histories, wearable technologies and personal health data, combined with the deep understanding of online and social media histories that can bring deeply integrated and personalized landscapes on individual patient and insight on disease prevention, diagnosis and intervention not previously thought possible. This makes "big data" (whatever the source) a genuine tool to allow our patients to have longer lives and better lives.

Will pathologists be simple facilitators and spectators of this third revolution? Will others in the medical profession drive adoption with pathologists (as it appears to be the case in most areas of molecular diagnostics) or will we be the leading actors in the play? Given that tissue pathology continues to stand the test of time and underpins many of these advances, and that pathologists are ideal integrators of data from a variety of sources [18], why can't pathologists embrace these advances and strive to change their profession for the better? The answer will be the difference between simply providing the raw image data for others to innovate and that of advocating the digitization of our services, or actively engaging in the creation and application of the diagnostic algorithms, validating technologies and overseeing the safe introduction of AI into diagnostic practice. Unfortunately, a degree of complacency is already

detected in our community, not dissimilar to the one we experienced in the molecular revolution. Our community would do well learning from experience, and become early adopters of the digitization and all that it means. The delivery of DP and the inevitable application of AI support will impact in how we make diagnostic decisions, the way pathology departments operate, driving and deriving improvements in and from IT infrastructure, storage and Laboratory Information System integration. Certified pathologists will need retraining and, just as importantly, organizations must seize the opportunity to modify and embed trainee/residency programs with new modules on DP and AI to prepare them for the next era of diagnostic pathology [6,7]. All revolutions are disruptive. Is it worth it?

Once again, the ball is in our court.

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Figure legends:

Figure 1: *Chronology of the "three revolutions" in pathology*. Abbreviations: DNA – deoxyribonucleic acid; IHC – immunohistochemistry; NGS – Next Generation Sequencing; FDA – Food and Drug Administration

Figure 2: <u>How Artificial Intelligence (AI) may, in the future facilitate multiple activities derived from the Hematoxylin & Eosin (H&E) sets of cases</u>. Today, these activities take up pathologist time in screening and annotation, whereas AI may perform all, report results to an appropriate part of the reporting pathway and/or to downstream laboratories to perform downstream tasks such as preparing extraction of nucleic acid for molecular testing based on automated annotation of the tumour stained by H&E. All activities would occur simultaneously upon scanning of the case H&Es stains.

Figure 3: *Steps in the Tissue Diagnostic Pathway*. Abbreviations: FFPE – formalin-fixed and paraffin-embedded tissue; H&E – Hematoxylin and Eosin stain; IHC – Immunohistochemistry; ISH – In situ hybridization, NA – nucleic acids