# Don't fear the future: Phenomics, Artificial Intelligence and Machine Learning in Cellular Pathology – Dr Tim Bracey

There are some exciting and frankly frightening things happening on the horizon which are likely to affect all of us, but particularly those of us who specialise in biological nanotechnology, i.e. cellular pathologists! In this article I am going to give an unapologetically biased account of some of the reasons why I don't think this is all doom and gloom and that AI and particularly phenomics are developments in pathology which will help rather than hinder us jobbing histopathologists. We are all aware of the NHS's recent interest in genomics, but I think that phenomics is going to be bigger and more powerful when this technology is fully realised. Phenomics (or my made up term "morphognomics") is the "big data" version of what we already do as pathologists, which is recognise patterns in tissues and translate those patterns into useful diagnostic, prognostic and predictive information for the patient. The examples to which I will refer are related to my own main interest (gastrointestinal cancer pathology) and rambling experience, but I have no doubt that this technology will soon permeate every branch of pathology, radiology and likely clinical medicine, surgery and general practice in coming years/decades.

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Traditionally our primary diagnostic report "lumps or splits" a patient's histology case into a particular diagnostic category. If we use the example of colorectal adenocarcinoma, we grade the tumour into well, moderate or poorly differentiated. We are all familiar with the tendency to use the middle grade more than the highest grade, and especially more than the lowest grade. The problem of course is related to the subjective nature of the grading process and the poorly defined boundaries between them. Most pathologists can confidently recognise a "typical" well differentiated and poorly differentiated tumour, but what is the worst differentiated adenocarcinoma that is still moderately differentiated? The books don't tell you, they just show you the average of each grade, and even then it is usually a single small medium to high power image. We also know that (with this example at least) that the treating clinician pays far less attention to histopathological

**Table 1. Definitions and abbreviations**

| | |
|---|---|
| Big data | Datasets (currently terabytes to petabytes) which are too large for traditional processing. |
| Genomics | The large scale mapping, quantification and characterisation of genes and genetic sequences. |
| Phenomics | Big data approach to study of the physical, morphological and biochemical traits of an organism, tissue or disease. |
| Artificial intelligence (AI) | An artificial system which mimics human intelligence in some way for example by learning, communicating or problem solving. eg. Apple Siri or Amazon Alexa. |
| Computer aided diagnosis (CAD) | A supervised task where a human helps the AI place an image in a diagnostic category. |
| Machine learning | AI systems which can learn and improve from experience without explicit programming or "stopping to ask why"! |
| Deep learning | A subset of machine learning which is a digital network capable of unsupervised learning from unstructured data. |
| Deep convolutional neural networks (DCNN) | Deep learning networks inspired by biological visual systems which learn to recognise features in images which can be extremely large and complex. |

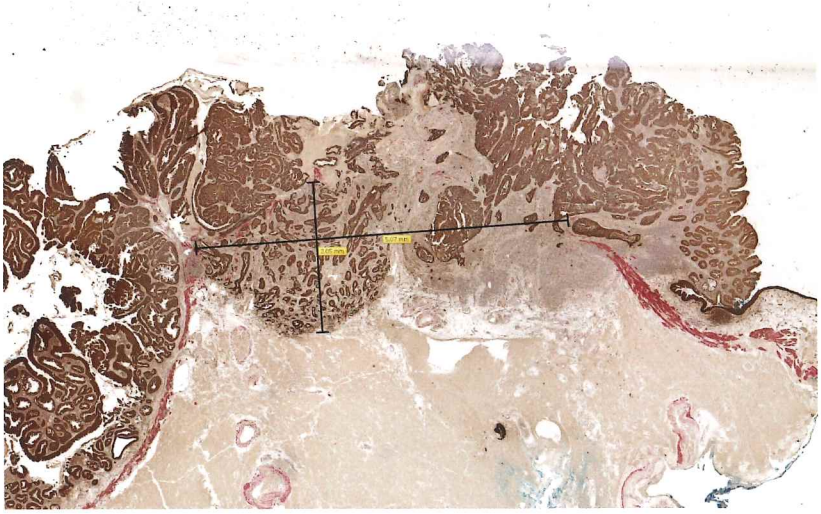

Figure1. A basic form of CAD measuring the depth and width beyond muscularis mucosae in a double stained (cytokeratin=brown, desmin=red) pT1 colorectal polyp adenocarcinoma. Width >4mm and depth >2mm beyond muscularis mucosae are associated with a significantly increased risk of lymph node metastasis.

grade than the TNM stage because in most cases, grade doesn't really affect management or show a particularly strong correlation with response to treatment or outcome. We have too much work to do to spend too much time on tasks which we know don't matter.

The current approach in the field of tissue phenomics is to use CAD (see table 1) image analysis algorithms more to identify features known to histopathologists, such as lymphovascular invasion, for example, to see if the AI can do better that a human observer. There are already some exciting examples of this approach in the literature showing impressive results even with small numbers of cases. It is notoriously difficult to predict the behaviour of patients with a postoperative Dukes' B stage in contrast to the extremely good prognosis of Dukes' A cases who need no further treatment, and Dukes' C patients virtually all of whom will receive adjuvant chemotherapy. Obvious extramural venous invasion in Dukes' B will usually prompt the oncologist to give adjuvant treatment but it is not always clear which patients should receive treatment, and outcome is still variable in this group. A recent study using CAD to identify tumour cell budding and lymphovascular invasion found that the Dukes' B cases could be reliably split into good and poor prognosis groups based on the character of the invasive border on a single microscopic image of each tumour[2]. I look forward to seeing the same approach being used on pT1 polyp cancers which always pose a difficult problem for surgeons determining whether the risk of lymph node metastasis (in many of these often indolent early cancers) is likely to exceed the risk of morbidity from major cancer surgery (see figure 1).

I think the most interesting developments are in the use of AI and machine learning for pathology images. Machine learning is where the AI is able to develop experience in recognising patterns, in a similar way to human visual learning. These so called "deep convolutional neural networks" will be familiar to smartphone and social media users; surprisingly sophisticated facial recognition algorithms have been developed using similar methods and now smartphone image archives can be searched for who or what is in the photograph not just by the name (see figure 2). Unlike

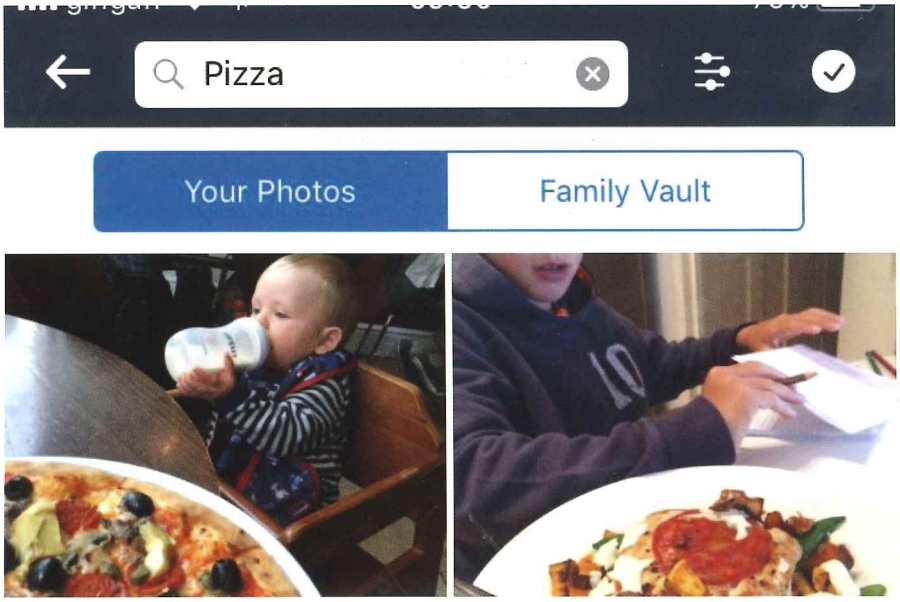


**Figure 2**. An example of DCNN image analysis from my smartphone family image archive. The AI can learn to find any common thing such as a pizza from an unlabelled archive but in the second image has even recognised a savory Hungarian lángos as looking "pizza-oid". Histology images can be probed in a similar way to identify known and novel features.

conventional programming, the AI is not instructed to specifically perform a task but learns them, akin to the visual systems in a biological brain, and unlike ourselves, does not get bored or distracted. Rather than focusing on features known to histopathologists, these DCNN's are starting to recognise novel features unknown even to the investigators. A recent publication for example has shown a reliable prediction of short and long-term survival in scanned microscopic images of non-small cell lung cancer, with the machine learning system identifying almost 10,000 quantitative features in the slides[3].

**Table 2. Examples of genetic or phenomic changes with histological correlate**

| Gene or Phene | Corresponding histological feature |
|---|---|
| Aneuploidy / chromosomal instability | Nuclear pleomorphism |
| Increased mitochondria. | Oncocytic or Hurtle cell change |
| Increased ribosomes and or RNA | Cytoplasmic basophilia |
| Increased proliferation | Increased mitoses, high MIB1/Ki67 immunostaining. |
| Cadherin/catenin loss | Non-cohesive / signet ring morphology or budding phenotype (EMT) when epigenetic alteration. |
| BCL2 overexpression | Reduced apoptosis and tingible body macrophages. |
| HPV driven SCC | Characteristic non-keratinising "basaloid" morphology and p16 overexpression in certain anatomical sites. |
| High MSI or EBV | Increased tumour infiltrating lymphocytes in gastric cancer |
| BRAF mutation | Nuclear grooves in thyroid and langerhans cells |
| Lymphatic invasion | Micropapillary pattern and inversion of glandular polarity |
| Mitotic spindle misorientation (PTEN dependent) | Cribriform pattern |

Going back to the facial recognition analogy, humans clearly have an incredible ability to recognise patterns and know we have seen them before. Histopathologists have always had this ability when seeing a characteristic tumour slide, but cannot always put the patterns recognised into sufficiently reliable words to allow another pathologist to recognise the same tumour without seeing it themselves first. Just as you might be able to recognise the face of someone who you haven't seen for 20 years, you are unconsciously recognising thousands of subtle features but your description of that person's face would be different to another observer looking at the same face.

Although our descriptions of complex patterns may not be particularly objective, we have an incredible ability to recognise characteristic histological patterns, which is clearly enhanced by visual training. I was fascinated to read an interview with the great Chris Fletcher in which he explained that he used to have lists in his office with names like "distinctly gelatinous thing on the leg", which he would gradually add to until he had enough cases to describe a new clinicopathological entity. Although his own initial description may have been vague, it was enough to tap into his own pattern recognition neural network to recognise the emerging entity again.

Some histological patterns are so characteristic that they can be recognised easily by even junior histopathologists, and the change in morphology can reflect an important biological property of the disease being studied with a corresponding genetic change. One example of this is the case of the signet ring cell phenotype in gastric cancer. I was fascinated even prior to training in pathology to hear that the signet ring phenotype (often recognised by the characteristic mucin vacuole pushing the nucleus to the side of the cell) could be induced in a conventional intestinal type adenocarcinoma *in vitro* by disrupting the E-cadherin gene. *In vivo* there can be a germline mutation leading to hereditary diffuse gastric cancer or in sporadic cases of diffuse gastric cancer, where expression can be variable throughout the tumour, epigenetic alteration can be responsible for the heterogeneous expression of the dyscohesive non-glandular phenotype[4]. Taken as a group compared with cohesive "intestinal type" gastric adenocarcinoma, signet ring/diffuse type adenocarcinoma has a tendency to spread to serosal surfaces and to be clinically under-staged. It also has a poor response, to conventional chemotherapy, with heterogenous tumours showing increasingly poor response dependent on the proportion of signet ring cells. Gastrointestinal adenocarcinoma and many other types of carcinoma of other primary sites show a marked tendency towards lymphatic invasion and

lymph node metastasis, dependent on the prominence of papillary, and in particular micropapillary, pattern on histological slides. It's not a great leap, based on some of the correlations seen between relatively crude subjective histological assessments and clinical outcome, to see that CAD and machine learning could probe not only the presence of these features but their frequency in tumours, to determine reliable prognoses and treatment response predictions.

In summary therefore I think phenomics has at least as much to offer as genomics; I would argue much more, since all epigenetic and post-translational changes result in morphological changes if they are biologically relevant. CAD will be the first technology to change our work as jobbing histopathologists by helping us to measure, count and quantify tumour and immunohistochemical results. I already frequently use a free online program to help me with MIB1/Ki67 counts and I would welcome an AI to help with the laborious time-consuming and subjective parts of my work, in particular cancer and dysplasia grading.

I don't think we have anything to fear from AI and CAD, but perhaps machine learning and DCNN poses more of a threat, only if we see having slightly less work to do as a threat! Once there is wholescale use of these algorithms, the "ground truth" of histological diagnosis will no longer be "the views of an expert somewhere" but the ground truth of patient outcome. I think there are exciting times ahead and this technology will show us what patterns are important, many of which I suspect will be related to the host immune response, stroma and tumour microenvironment, not just the tumour cells. Plus I think it will be nice to be able to give orders to brainless machines like "Alexa! get me more coffee", "Siri! check I haven't missed anything in these 30 sections of prostate chippings", "Surgeon! Cut out this tumour" ...


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2. Caie PD, Zhou Y, Turnbull AK, Oniscu A, Harrison DJ. Novel histopathologic feature identified through image analysis augments stage II colorectal cancer clinical reporting. Oncotarget. 2016;
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