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Automation of diagnostics by new disruptive technologies supports local general practice and medical screening in the third world

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EDITORIAL

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It was recently observed that the percentage of doctors working in primary health care has dropped from 41 per cent in 1999 to only 35 per cent in 2009, with an associated increase in medical specialists.[1] Coupled with an aging cohort of doctors, general practice has many future challenges, with some suggestions, such as substitution by nurses and pharmacists, fuelling the ongoing debate about its future. More importantly, shortages are now greater in areas classified as rural, remote, or disadvantaged, and in third world regions. Emerging technologies in medical diagnostics, however, may slow or even reverse the drift to increasing specialisation. Examples are presented for three important new disruptive technologies that are already entering service and which may have a very significant impact on medical diagnostics delivery and the healthcare industry, including current business models.

Fast portable blood tests with micro-samples

The pathology business for diagnostic blood tests has been challenged recently by Theranos, a new company from Palo Alto, California, in the United States (US).[2,3] The new disruptive technology can analyse a drop of blood from a single pinprick, as opposed to traditional syringe aspiration producing multiple 13cc vials. More than 30 tests are possible on a single sample with rapid assessment of common indicators of lifestyle diseases, without suffering the physical discomforts of syringe aspiration. Single-prick testing is less invasive and uses *microfluidics* apparatus with smart AI software, a new field of technology associated with DNA chips and lab-on-a-chip hardware.[4] Results are available in less than four hours rather than three days, meaning that the patient can have a single micro-sample drawn early in the day and see the doctor for diagnosis a few hours later. The speed and cost reduction (by half) means that pathology cost and federal funding could be greatly reduced. With further development, blood diagnostics for some tests may be effectively real-time. All that is required is a single draw of 25–50µl in a nano-vial the size of an electric fuse.[3] The entire process can be carried out in the general practice rather than in an external laboratory.

The disruptive effect of the Theranos technology is hard to underestimate.[2] It would benefit those who need frequent blood draws, such as cancer sufferers, as it is fast and less invasive and would improve the speed of response to postoperative infections. For example, using DNA profiling, it is claimed that the technology can identify infection source and its resistance profile within four hours, rather than several days, with a huge influence on the treatment of hospital-acquired infections.[3]

It was reported in the financial press that a recent capital raising by Theranos effectively valued the private company at USD $9 billion,[2,3] if floated, in comparison to USD $7 billion ascribed to Sonic Healthcare, the major player in traditional blood pathology in Australia. Furthermore, it has been suggested that switching to the new technology can produce savings of USD $200 billion over a decade to US Medicare and Medicaid, which has implications also for health funding policy in Australia. The Theranos diagnostics business is vertically integrated and there is no indication of supply of the technology yet to third-party pathology laboratories, which suggests a potential threat to the current pathology industry in Australia. There are, however, competitive technologies emerging that are similar and will compete with Theranos.[5]

Retinal imaging

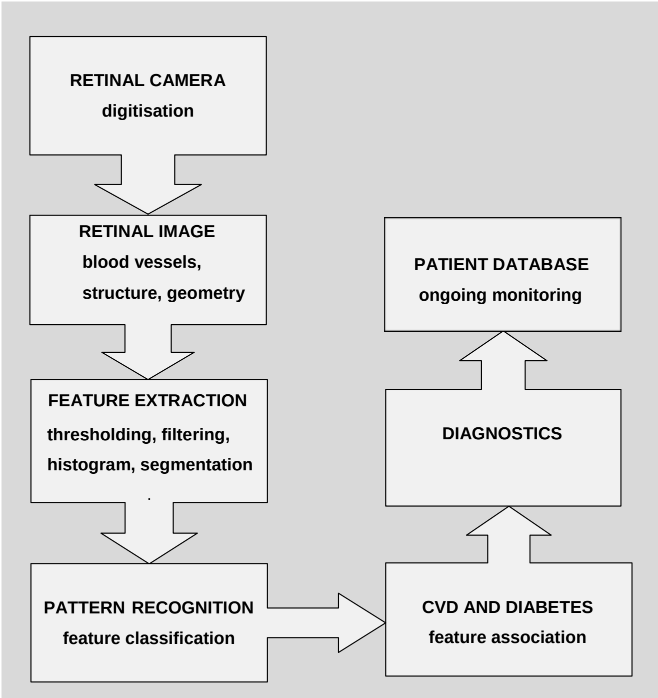
Heart disease, high blood pressure, stroke, and diabetes are all major causes of death and disability in Western society.[6,7] More effective screening for these conditions would have an impact on cost-benefit analysis with respect to public health and federal funding. Automated retinal imaging with digital image processing and pattern recognition software can be used to analyse the condition of blood vessels and provide markers of early blood vessel damage.[8,9] The advantage of early cardiovascular disease (CVD) prediction supports timely preventative action, such as dietary changes and lifestyle adjustments.

Commercially available retinal cameras are used widely by ophthalmologists for eye disease diagnosis and also increasingly for screening by optometrists during eye testing for spectacles. Aside from detection of eye disease, retinal vascular features and their changes over time may be associated with chronic lifestyle disease predictions at the asymptomatic stage.[6] It is not uncommon for diabetes to be detected by the ophthalmologist during an eye examination in the form of diabetic retinopathy. Retinopathy signs (microaneurysms, bleeding, oedema) are also associated with stroke, hypertension, heart failure, peripheral vascular disease as well as diabetes.[6–8] Similarly, measurable retinal features that correlate with potential disease include retinal vessel diameter (RVD), e.g., arteriolar narrowing, retinal venular widening, and arteriolar tortuosity.[6]

The reason for correlation between changes in vascular image structure in the retina and CVD has been the subject of ongoing research.[7–9] It is generally thought that small blood vessels in the choroid may respond differently to oxidative stress than larger systemic vascular structures characteristic of large organs. The RVD has been associated with oxidative stress and has been investigated for relationships with ocular and systemic diseases.[6–9] The Beaver Dam Eye 20-year longitudinal study suggested an association between RVD and inflammation markers (such as C-reactive protein), medication, diet, and age-related macular degeneration.[9]

A retinal camera with pattern recognition software can quantify the disease markers and associate the features with risk of CVD and diabetes from population studies.[6] Following image digitisation, algorithms are used for vessel calibre measurement and feature classification, which are then associated with the disease states to produce a prototypical expert system. The process is summarised by the flowchart in Figure 1. (Also, see the review by Bhuiyan et al.[8])

Figure 1: Pattern recognition flowchart for analysis of damaged micro-vasculature in the retina



Retinal markers include blood vessel retinopathy symptoms, tortuosity, venous nicking, arteriolar narrowing, and venular widening. Retinal markers are correlated with higher risk for cardiovascular disease and diabetes.[7,8]

The technology of using a retinal camera with smart software also has potential for early inexpensive detection and monitoring of CVD and diabetic retinopathy in remote regions and the third world.

Plasmonic ELISA

An inexpensive new methodology for detection of disease biomarkers at ultralow concentrations has been described by de la Rica and Stevens.[10] The approach is referred to as plasmonic ELISA and can detect as little as a few molecules of a substance by the naked eye. It is suitable for locations where resources are sparse, such as third world countries. It has been suggested that plasmonic ELISA could aid in the early detection of cancer, infections, or neurological diseases.[11] The process has the characteristics of being analyte-specific, with low limit of detection, cost effective, and suitable for automation.

The new diagnostic tool is based on signal generation methodology and ultrasensitive biosensing involving enzyme-linked immunosorbent assay (ELISA), where a sequence of biochemical reactions generates a signal that is a measure of the analyte present in the sample. Plasmonic ELISA combines ELISA and surface plasmon resonance of gold particles. It is a process characterised by the growth of gold nanoparticles in solution, mediated by hydrogen peroxide concentration, to generate coloured solutions for rapid *visual matching* with the analyte of interest,[10] such as prostate specific antigen (PSA), or HIV-1 capsid antigen p24. The limitation of the technique is that, although it can detect the target molecule in concentration as low as $1x10^{-18}$g/ml^{-1}, it is inaccurate in quantification—that is, it is suitable for ultrasensitive detection rather than dose estimation.

In experimental trials, naked eye detection of p24 was accomplished in serum using HIV-infected patients with viral loads not detectable by a gold-standard nucleic acid-based test.[10,11] Using plasmonic ELISA, HIV-positive donors produced nanoparticle dispersions characterised by a blue colour, whereas HIV-negative donors produced dispersions characterised by a red colour. Plasmonic ELISA could be further improved by integration with microfluidic technology for in-field measurements of blood or plasma.[4,10] The added benefit for such ultrasensitive and inexpensive diagnostics technology is application to remote regions, where there are few specialists, such as Sub-Saharan Africa.

Summary

The technologies described are spreading beyond the research laboratory into the commercial world.[2,3] There are three salient features of these new and disruptive technologies, especially with respect to healthcare innovation as a goal to support general practice.[12,13] First, the low-cost, ultra-sensitive, and real-time nature of the technologies provide special benefits to rural and remote regions, and especially in the third world, where there is a shortage of general practitioners. Second, they offer new lines of professional activity and business for general practitioners, in many cases without the need for further referral and expert opinion. Third, they challenge current business models on the delivery of pathology, especially blood diagnostics. Because of this, there may be upheaval in the diagnostics industry in the future following reappraisal of current business models in the face of these emerging technologies.[2,3]

Automation of diagnostics may slow the trend to increasing specialisation simply because new technology and smart software will allow general practitioners to make decisions that, in many cases, previously required referral to specialists. Although this could slow or even counteract the trend towards increasing specialisation, it may, however, support another threat to general practice. Automation of diagnostics will add to the ongoing debate on identifying the *boundary* between general practice and pharmacy or nursing. In the state of Victoria in Australia, a parliamentary enquiry has been investigating the issues and the potential role of pharmacies in primary and preventive health care, including dispensing of vaccinations.[14] In this respect, the Australian Medical Association may eventually recommend that any greater role by paramedics in diagnostics be overseen by general practitioners.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.