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Contents

Expanding decentralised healthcare: Lab-grade CBC testing at the point of care

Despite a global trend of decentralised healthcare, robust complete blood count (CBC) diagnostics remain in central laboratories. Sight Diagnostics presents a groundbreaking alternative – Sight OLO®, an AI-driven haematology analyser that enables decentralised healthcare with lab-grade accuracy and speed at the point of care.

Support for the development of this article was provided by Sight Diagnostics

With the rise of telemedicine and home-based care, healthcare is increasingly becoming decentralised. And due to the recent challenges catalysed by the COVID-19 pandemic, this need for patient-care models outside of traditional hospital settings has intensified – calling for innovative care pathways, especially in decentralised locations.[1]

Although most diagnostic technologies – blood gas, urinalysis, blood glucose monitoring, infectious markers, etc – have transitioned to various point of care (POC) offerings, CBC testing still occurs in laboratories with high operational overheads. This is primarily due to technical limitations requiring highly trained operators and expensive laboratory equipment with a special set-up for daily quality control, calibration, reagent management and liquid waste disposal. But given the ubiquitous nature of CBCs, the lack of fast and accurate CBC analysers in POC settings prevent care modalities from providing the best treatment.

According to Tony Cambridge, the lead biomedical scientist in the pathology management team at the University Hospital Plymouth NHS Foundations Trust, the healthcare community is on the cusp of a pivotal breakthrough to bring testing closer to patients. Cambridge further asserts that community-based diagnostics – if stewarded correctly – can reform problems in the health services landscape, such as growing waiting lists, care delays, accumulating costs and undesirable patient outcomes.[1] Since legacy haematology processes are rife with similar limitations and CBCs play such a critical role in ensuring adequate care, there is an urgent call for CBC diagnostics to join in the decentralised healthcare movement by reimagining the clinician–patient experience.

> “Diagnostics offered closer to the patient are in no way designed to undermine the service provided by pathology laboratories, but to enhance it, and safeguard optimal care for the patient. Used in an appropriate way, decentralised testing can reduce pressure on support services, such as pathology and phlebotomy, by redirecting workload to other workstreams, preserving the laboratory testing for specialist and urgent hospital cases.
>
> Tony Cambridge, lead biomedical scientist in the pathology management team, blood sciences and point of care testing at the University Hospital Plymouth NHS Foundations Trust[1]

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Figure 1. Sight Diagnostics OLO self-contained haematology analyser

Important considerations for the adoption of CBC technology in decentralised settings

To enable care providers to efficiently and effectively run their operations while providing high-quality treatment to patients whenever – and wherever – there are a few standards POC CBC technology needs to uphold:

Achieving high accuracy for all CBC parameters

Currently, the majority of POC CBC analysers are miniature versions of legacy analysers. However, due to the simplification required to downscale this technology, the accuracy often gets affected, resulting in only a few FDA clearances for POC CBC analysers of late.[2] Consequently, additional tests are required to confirm the accuracy of the test results, causing the drawing of more blood, which in effect delays – rather than speeds up – the entire process.

Sight OLO is an innovative haematology system designed to address these current limitations in POC blood diagnostics (Figure 1). By leveraging innovations in physics, optics, sample preparation, and AI-driven computer vision technology, the self-contained quantitative multi-parameter analyser digitises blood samples to deliver five-part differential CBC results with 19 parameters and sophisticated flagging capabilities at the point of care.

During a Sight study published in July 2021, the accuracy of OLO was compared with the Sysmex XN-1000 System. Samples – covering a broad clinical range for each tested parameter from 355 males (52%) and 324 females (48%) aged 3 months to 94 years – were analysed. The regression analysis results showed a consonance in correlation coefficient and slope, bias and intercept between OLO and Sysmex XN. Therefore, the study concluded that OLO performs with lab-grade accuracy for all CBC parameters (Figure 2).

Reference

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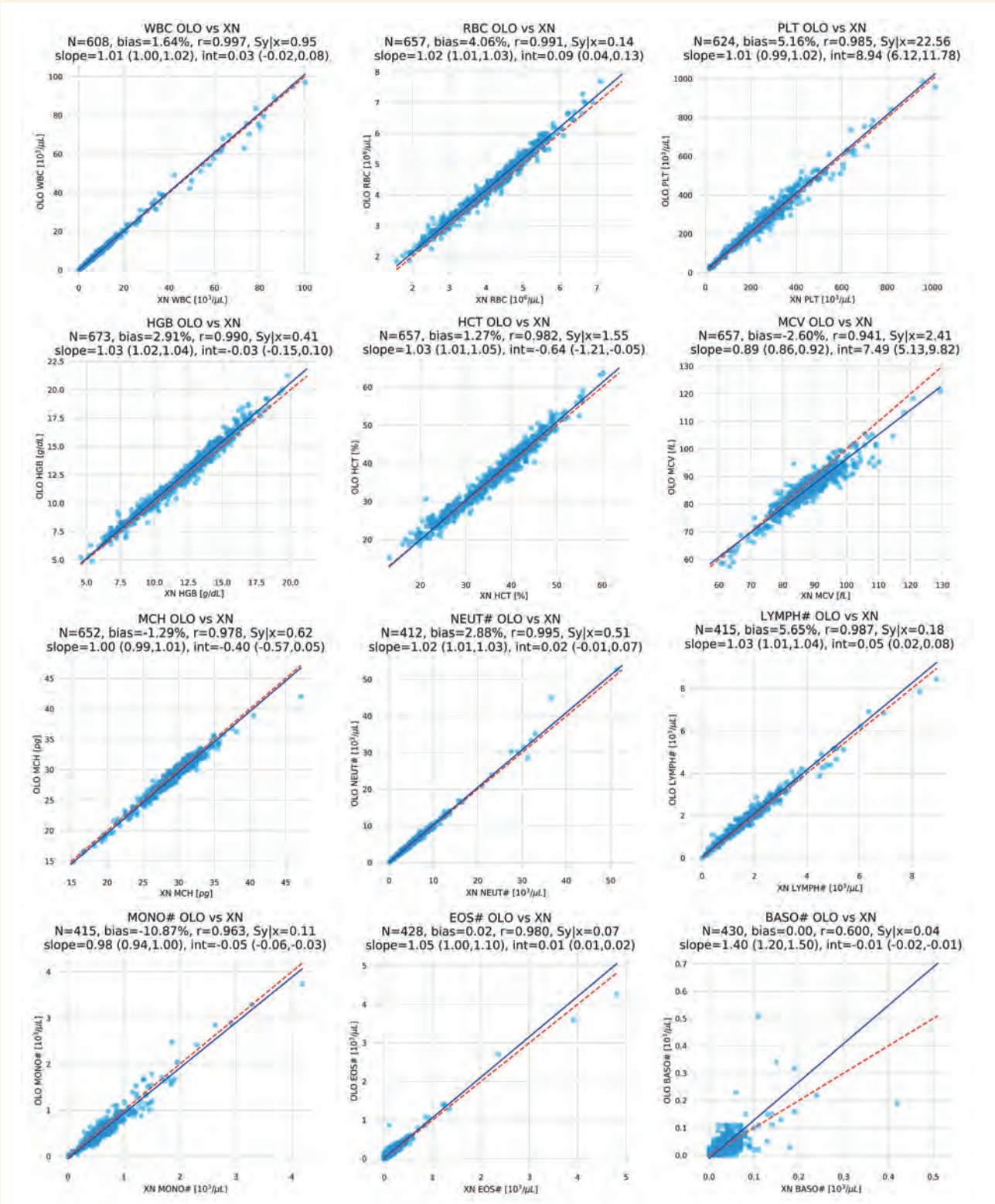
FIGURE 2

Meta-analysis plot graphs displaying the results of a method comparison study between the Sight OLO and the Sysmex XN haematology analysers. Graphs indicate Pearson correlation, slope and bias for each parameter. *From AJH 2021;96(10):1269*



Prioritising sampling convenience, accessibility and turnaround time

Traditional blood testing requires a phlebotomist to draw vials of blood through venipuncture – a time-intensive and highly skilled process – which can pose challenges in near-patient settings. Thus, for CBC testing to work in decentralised conditions, the system's sample preparation process must empower care providers, not necessarily skilled phlebotomists by trade, to effectively sample a patient's blood. Additionally, it is essential for the sampling methods to be accessible to sensitive patients in delicate situations, i.e., babies (older than three months), elderly patients with difficult veins and patients with mental health problems (especially patients diagnosed with schizophrenia).

Sight OLO is the first CBC analyser that is FDA 510(k) cleared for blood taken directly from a finger prick. Each test requires just two drops of blood from a finger prick, making OLO convenient for healthcare workers and accessible to sensitive patients aged three months and above. Furthermore, operators can complete this sampling process in under one minute and obtain the full results in minutes.

Amid one study conducted in November 2020 in an oncology day centre in Israel, Sight evaluated OLO's accuracy for finger prick samples across the OLO reportable range. The study results showed high correlations between the finger prick results of OLO vs the venous results of OLO (Table 1). During the study, Sight also tested the device's turnaround time compatibility to the centre. An OLO and Beckman Coulter DxH800 (the centre's current system) comparison revealed that OLO decreased the average time from phlebotomy to CBC results by 45%.

TABLE 1

A table from the finger prick matrix study at an oncology centre in Israel presenting the correlation, slope, intercept and bias retrieved for each CBC measurand, for the comparison between the mean of two finger prick results on OLO vs. the venous results of OLO.

Measurand	N	Range	Correlation	Slope	Slope CI	Intercept	Intercept CI	Relative bias	Absolute bias
WBC [x10³/µl]	52	1.6 to 22.7	0.983	1.03	(0.96, 1.11)	0.071	(-0.270, 0.372)	4.7	0.240
RBC [x10⁶/µl]	52	2.2 to 6.0	0.964	1.01	(0.94, 1.10)	-0.097	(-0.422, 0.177)	-0.8	-0.035
PLT [x10³/µl]	46	45.0 to 413.0	0.940	0.95	(0.88, 1.05)	-0.1	(-14.7, 12.2)	-4.6	-7.3
HGB [g/dl]	53	6.8 to 17.9	0.952	1.00	(0.92, 1.11)	-0.15	(-1.37, 0.78)	-1.4	-0.15
HCT [%]	52	20.1 to 53.4	0.952	1.02	(0.94, 1.11)	-0.9	(-4.11, 1.68)	-0.6	-0.20
MCV [fl]	52	73.0 to 117.6	0.994	0.98	(0.95, 1.01)	2.21	(-1.06, 4.92)	0.2	0.18
RDW [%]	51	12.4 to 22.0	0.979	1.04	(0.97, 1.10)	-0.55	(-1.50, 0.46)	0.0	0.00
MCH [pg]	52	21.9 to 38.2	0.998	1.00	(0.99, 1.02)	0.00	(-0.59, 0.31)	0.0	0.00
NEUT% [%]	53	19.4 to 88.5	0.970	1.03	(0.97, 1.09)	-2.19	(-6.01, 2.31)	-0.1	-0.05
NEUT# [x10³/µl]	52	0.5 to 19.6	0.989	1.04	(0.97, 1.11)	-0.010	(-0.169, 0.175)	3.5	0.115
LYMPH% [%]	44	5.1 to 75.3	0.976	0.97	(0.91, 1.04)	0.89	(-0.28, 2.29)	2.5	0.50
LYMPH# [x10³/µl]	43	0.4 to 13.8	0.984	1.15	(1.04, 1.30)	-0.056	(-0.223, 0.083)	10.9	0.130
MONO% [%]	35	2.2 to 15.7	0.906	0.90	(0.75, 1.05)	-0.30	(-1.24, 0.93)	-15.4	-0.85
MONO# [x10³/µl]	35	0.1 to 1.8	0.887	0.90	(0.74, 1.10)	-0.004	(-0.068, 0.053)	-11.5	-0.030
EOS% [%]	39	0.1 to 6.3	0.937	0.96	(0.87, 1.06)	0.02	(-0.09, 0.22)	-2.9	-0.05
EOS# [x10³/µl]	39	0.0 to 0.4	0.941	1.00	(0.85, 1.10)	0.010	(-0.001, 0.016)	8.7	0.010
BASO% [%]	39	0.0 to 3.1	0.701	0.80	(0.45, 1.07)	0.00	(-0.07, 0.12)	-20.0	-0.05
BASO# [x10³/µl]	39	0.0 to 0.1	0.555	0.50	(0.33, 1.00)	0.010	(0.000, 0.013)	0.0	0.000

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**There is no manufacturer requirement for QC. Additional QC may be required according to local regulations*

Scaling CBC technologies for decentralised settings

When traditional CBC analysers are merely miniaturised, they often inherit "many of the product attributes of their larger relatives, including the requirements for liquid reagent replacement, washout and calibration procedures, and frequent quality-control processes which in the POC context can be limiting or prohibitive."[2] Therefore for CBC technology to scale for use in decentralised environments, all the accompanying attributes must be addressed.

Sight OLO is perfectly suited for POC in various clinical settings. It has a small footprint (284mm x 254mm x 323mm), and the analyser comes factory calibrated for a quick set-up, requires no maintenance or quality control*, and only needs a power outlet. Hence the device requires no scheduled downtime, is always "on" without needing time to warm up or shut-down and does not necessitate a skilled lab technician to operate the device. Additionally, OLO uses one disposable cartridge per test, which can be stored without refrigeration and has a shelf life of over a year. thus eliminating the need for reagent procurement, hazardous material storage and liquid waste disposal, rendering the device suitable to be placed on any stable surface.

At the beginning of 2019, Sight conducted a usability study to test the ease of usage and training and determine users' consequent understanding of the Sight OLO system. "In this observational study, 16 participants, representing a wide variety of potential operators, easily, safely, and effectively performed all critical tasks for the intended use of the OLO device when provided with the level of training and documentation provided in standard commercial use".[3] During the usability study, Sight also concluded that OLO's internal Failsafe designs — to mitigate significant risks and operator errors — are all adequate and effective. And that "no use errors, task failures, or user interface shortcomings encountered will lead to an unacceptable level of harm to the patient, environment, or operator."[3]

For ease of oversight at decentralised locations – beyond Sight OLO's internal Failsafe mitigations, ease of use and training – OLO's technology also enables lab managers to set different access permissions for various operators with varying experience and trace operator activities.

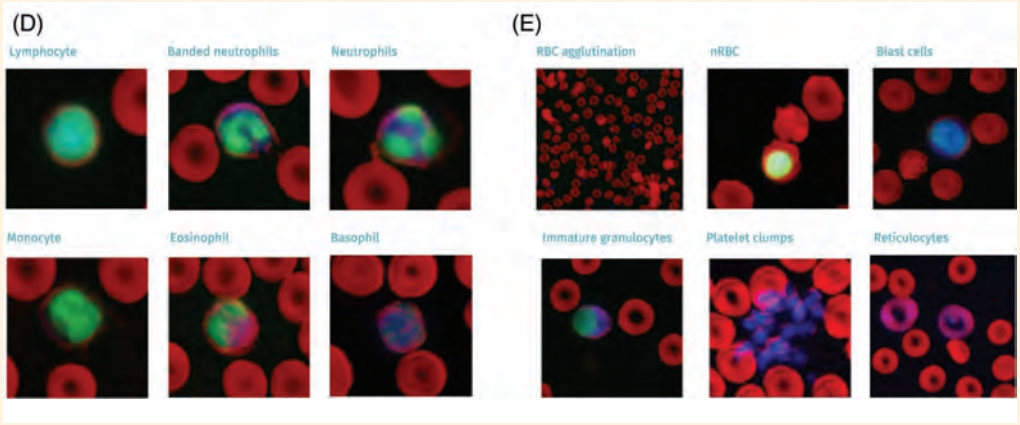
Reimagining CBC blood diagnostics

It has become evident that for CBC testing to work in decentralised settings, it is vital to reimagine the entire CBC diagnostics principle.[2] As an innovator, Sight Diagnostics investigated how legacy laboratories utilise microscopists to review out of range or invalidated results produced by their analysers. To address these limitations and ensure high quality and consistent results, Sight created a digital microscopy approach with an AI-trained algorithm. After years of research, Sight Diagnostics' use of computer vision and AI represents this digitised CBC leap within the POC space, consequently eliminating unnecessary reflex and wasted time.

According to Yossi Pollak, the co-founder and CEO of Sight Diagnostics, OLO's system takes two drops of blood and automatically creates a monolayer of cells within the self-contained cartridge. Once the specimen cartridge is placed inside the analyser, the device captures over 1000 images within minutes, turning the blood sample into a set of high-resolution digital images. Then – in real-time – the device uses AI to classify, enumerate and identify anomalies in the blood samples to produce the final CBC results.[4] Imagine the same microscopist all day, every day, providing gold standard results; that's OLO.

FIGURE 3

The Sight OLO haematology analyser. (D,E) False-coloured micrographs collected using OLO's multispectral microscopy. Red channel: haemoglobin absorption; green channel: nuclear DNA fluorescence; blue channel: cytoplasmic staining. (D) Characteristic examples of different white blood cell types. (E) Characteristic examples of different anomalous cell types and formations. *From AJH 2021;96(10):1266*

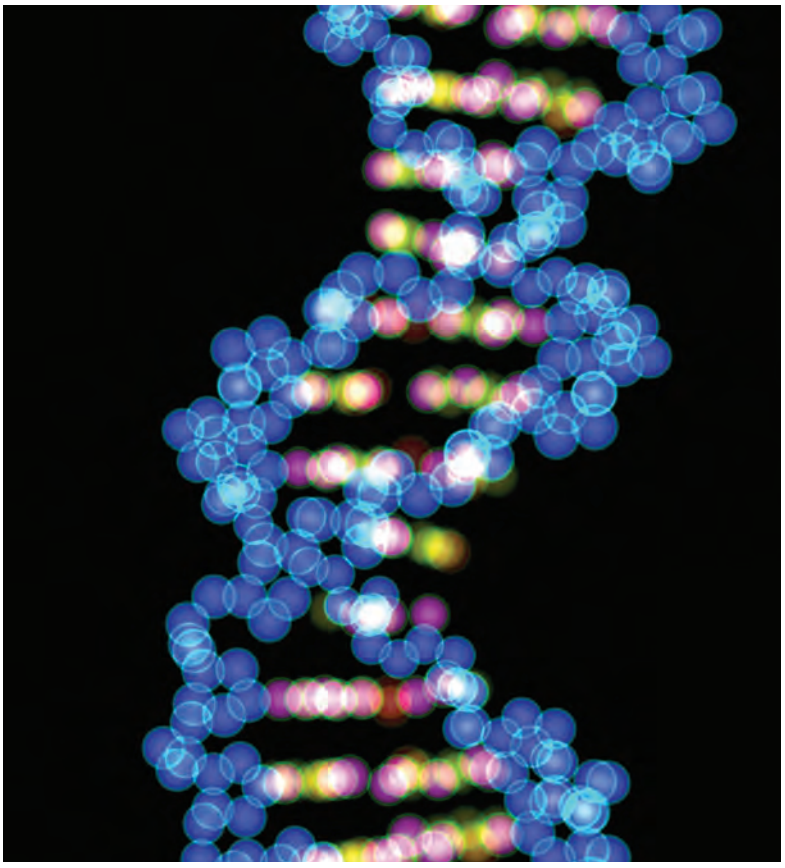


Building on Sight OLO's excellent performance in POC settings, Sight constantly evolves OLO's AI-powered CBC models as well as exploring ways to expand on the application of OLO's underlying technology. For example, machine vision-based technology enables the digitalisation of blood samples into image data. This image data will continue to fuel further research and development efforts into clinical conditions with visual signatures in the blood samples.

Overall, Sight Diagnostics has successfully responded to the call for CBC testing to decentralise healthcare and bring diagnostics closer to patients. Now is the time for CBC-reliant health services and laboratories to implement this pioneering technology and follow suit.

OLO is CE Marked according to the IVD European directive for performing CBC tests in point of care settings. The device is also FDA 510(k) cleared for use in moderately complex settings in the United States. For full indications for use and safety information, please visit the Quality and Compliance page at www.sightdx.com.

100,000 Genomes Project identifies genetic diagnosis in patients with rare diseases



The 100,000 Genomes Project, which involves whole genomic sequencing, has led to a new diagnosis in 25% of patients with a rare genetic disease.

A rare disease is defined as one affecting fewer than 1 in 2000 people in Europe[1] and while much progress in recent years has enabled the identification of the genetic basis of many rare diseases, the underlying cause remains to be determined in at least half of these diseases. In an attempt to better understand the genetic basis for rare diseases, the 100,000 Genomes Project was established in the UK in 2017.[2]

The 100,000 Genomes Project trialists are a group of UK researchers from various locations and who have performed a pilot study to investigate the value of whole genome sequencing in patients with an undiagnosed rare disease.[3] The investigators included patients with an undiagnosed rare disease which had not been diagnosed after receiving usual care in the National Health Service. For the genomic sequencing, the researchers investigated both coding and non-coding regions of DNA to identify 'novel diagnostic variants' in genes that had not been previously described in the literature.

Findings

The pilot enrolled 4660 participants which included 2183 probands (i.e., the first individual to receive any genetic counselling or testing) with a median age at recruitment of 35 years, of whom, 52% were male and 2477 family members. A wide range of rare diseases were included, involving neurological, ophthalmologic, dermatological and those representing intellectual disability and a metabolic disorder.

Based on whole genomic sequencing, the researchers were able to make a genetic diagnosis in 25% (535/2183 cases) of probands, of which 60% (322/535) were made on the basis of coding SNVs (single nucleotide variants) or indels (insertions and deletions) in the applied panels; additionally, 26% (141/535) were established based on coding SNVs or indels affecting well established disease genes outside of the applied testing panels. Furthermore, 10% of the probands had a variant of unknown significance in genes determined by geneticists at the recruiting site. The highest clinical categories of diagnostic yield were neurologic or development disorders (653), ophthalmologic disorders (321) and renal or urinary tract disorders (175).

The researchers identified that 35% of genetic diseases were considered to have a monogenic cause and 11% a more complex cause. A further important finding was that the 25% of genetic diagnoses (i.e., 134/535) were reported by clinicians to be of immediate clinical actionability and of value to patient care, for example, eligibility for a gene-replacement trial, whereas only 0.2% were described as of no benefit.

The authors concluded that their study supported the case for genomic sequencing in the diagnosis of certain, specific rare diseases and hoped that these findings would enable other healthcare systems to consider genome sequencing for patients with rare diseases.

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AI system successfully detects colorectal cancer from tissue scans

The development of an AI system that was able to successfully detect cases of colorectal cancer with a similar accuracy to experienced pathologists is an important breakthrough in the diagnosis of this condition.

Globally, colorectal cancer (CRC) is the third most common cancer in men and the second most common in women, with over 1.8. million cases diagnosed in 2018.[1] CRC is diagnosed by pathologists after a digital examination of a full-scale whole slide image (WSI). However, a major diagnostic challenge is the complexity of these WSIs; in particular, their very large size (>10,000 x 10,000 pixels), complex shapes, textures and histological changes after staining, all of which make the diagnosis both complex and time-consuming. In addition, with a recognised international shortage of pathologists combined with increasing levels of cancer, necessitates the introduction of supportive systems to help manage the workload. One increasingly used form of support is artificial intelligence systems, based, for instance on deep learning (DL). In fact, DL systems have already helped in the classification of CRC types,[2] detection of tumour cell type[3] and even prediction of survival outcomes.[4]

Using a supervised learning (SL) recognition system for CRC, a team from Department of Biomedical Engineering, Hunan, China, developed an AI system which was highly accurate for the diagnosis of CRC.[5] Nevertheless, an accepted limitation to their system was that it was built using patches of scans previously labelled by pathologists but in practice, scans are often no comprehensively labelled which reduces the utility of the system in a real-world setting. In an effort to refine their system, the researchers investigated the value of semi-supervised learning which does not rely as much on labelled data.

For their current study,[6] the team used 13,111 WSIs collected from 8803 patients to train and test the semi-supervised learning (SSL) model. It was evaluated by comparison with an SL model for patch level recognition, with patient level data and with experienced pathologists. In trying to further demonstrate the value of their SSL model, the team used samples of lung cancer and lymphoma and used the area under the receiver operating characteristic curve (AUC) to assess the performance of their model.

Findings

When comparing the SSL and SL model for patch-level recognition, the SSL model was superior, with the corresponding AUC values being 0.91 vs 0.79 (SSL vs SL, p = 0.017). Again, with patient-level data, the SSL model was superior with AUCs of 0.97 vs 0.81 (SSL vs SL, p = 0.002). Finally, the SSL model was comparable to that of six experienced pathologists, with AUCs of 0.97 vs 0.96 (SSL vs pathologists). Using both lung and lymphoma samples the SSL model was able to achieve similar performance to the SL model.

In discussing these findings, the authors commented on how their SSL model was able to outperform the SL model at patch-level recognition, even when there was only a small amount of labelled data. They added that the patient level data suggested that the SSL model might not require as much labelled data as the SL model.

In their conclusion, they felt that future work needs to focus on annotation and more effective use of unlabelled data to improve the efficiency of AI systems.

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CTCs could be a potential biomarker for treatment resistance with docetaxel

Analysing the amount of circulating tumour cells in blood prior to initiating treatment with docetaxel could serve as an important biomarker for the prediction of treatment response.

Measurement of circulating tumour cells (CTC) could be used as a biomarker to predict the treatment to docetaxel in men with advanced prostate cancer. This was the finding of a study by a team from Barts Cancer Institute, London, UK. Docetaxel is recommended as a treatment option for men with hormone-resistant metastatic prostate cancer (mHSPC) as it improves overall survival (OS) and time to disease progression.[1] The drug is also effective in metastatic castration-resistant prostate cancer (mCRPC).[2]

However, not all patients respond to chemotherapy with docetaxel and some become treatment-resistant. The team from Barts wondered if it was possible to somehow identify those patients who would become treatment resistant. They turned their attention to circulating tumour cells (CTCs), which are a subset of cells in the blood which serve as a metastatic seed for cancer as it spreads. The researchers collected blood samples from patients with both mHSPC and mCRPC and used the Parsortix system to separate the CTCs from the blood sample.[3]

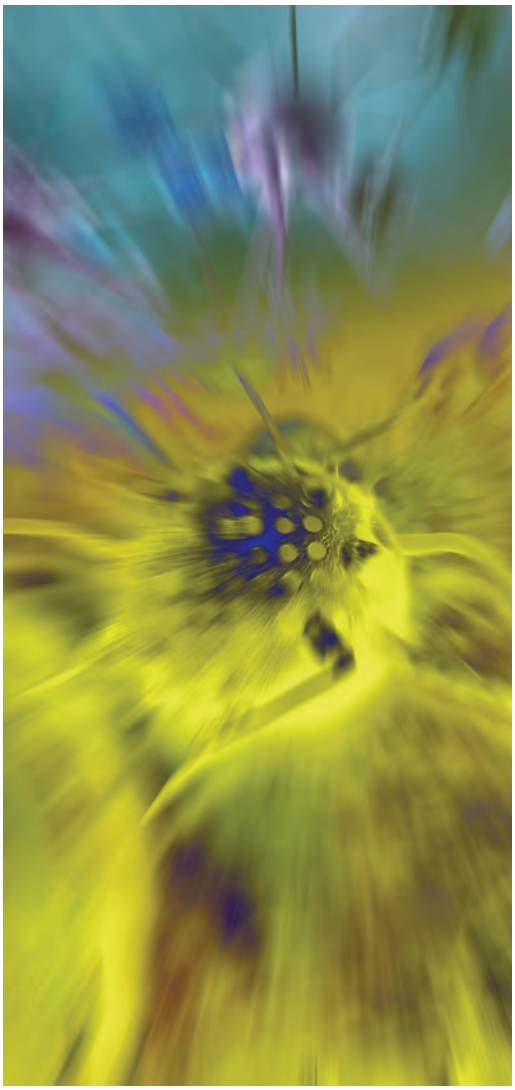
Findings

A total of 56 men with advanced prostate cancer were included and at total of 205 CTCs samples were obtained from 44 mHSPC and 12 mCRPC patients. The presence of CTCs were detected in 61% of samples and 75% of patients with progressive disease (PD) had a positive CTC score prior to docetaxel chemotherapy.

Analysis of pre-chemotherapy CTCs revealed a significant inverse correlation of CTC parameters with OS and progression-free survival (PFS). A CTC positive score and in particular, the presence of several subtypes of CTC (e.g., cytokeratin, CK) had the most significant correlation with overall survival. For instance, in mCRPC patients, the correlation of CTC score with OS was -0.85 ($p = 0.0095$), as was a high total CTC number and OS (-0.69, $p = 0.031$). In addition, the number of CK+CTCs were significantly correlated with OS in both mHSPC and mCRPC (-0.46, $p = 0.0013$).

Using Kaplan-Meier analysis of CTCs before chemotherapy showed that both a positive CTC score and the presence of greater than 1 CK + CTC, significantly predicted poor OS in both prostate types ($p = 0.011$) and OS ($p = 0.0018$) and progression-free survival ($p = 0.024$) in mCRPC alone. In contrast, with greater than 5 CTC was the best predictor of poor OS ($p = 0.019$) in mHSPC.

In conclusion, the researchers wrote that 'These findings provide a promising potential solution to predicting and monitoring DOC resistance using a non-invasive and easily repeatable system.'



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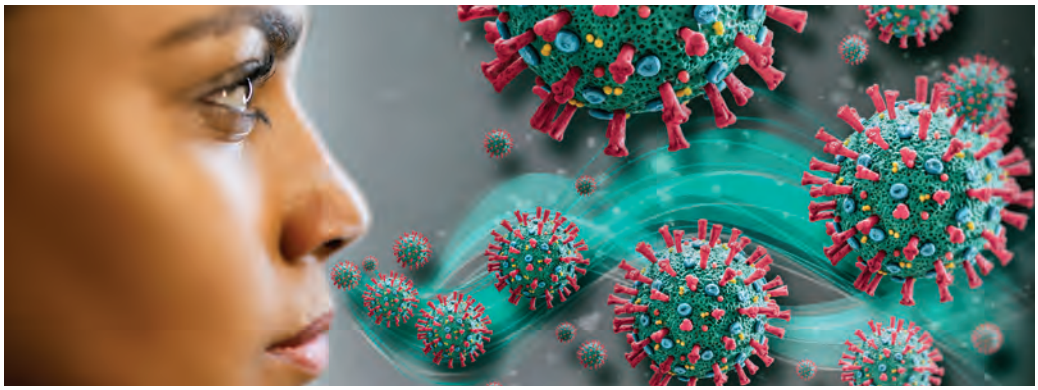
Nitric oxide breathalyser for COVID-19 shows high level of accuracy



A novel breathalyser that makes use of a reaction between nitric oxide, oxygen and ammonia to create a unique breath print can be used to identify patients infected with COVID-19.

This is the conclusion from a study by a team from Department of Internal Medicine, The Ohio State University Wexner Medical Center, Ohio, United States.

In patients with a viral infection, the inflammatory response leads to be production of several volatile compounds which can serve as biomarkers for the disease.[1] These volatile compounds can be identified with electronic detection devices (so-called 'e-noses') which contain an array of sensors that are optimised for a different chemical range. For example, an e-nose makes use of nanoparticle sensors which contain organic molecules with functional groups that react with volatile organic compounds in a breath sample, leading to a volume change such as swelling or shrinking, and which can be subsequently detected by a sensor.[2]

But rather than relying on a multiplex-array for the detection of volatile compounds in breath, the US team developed a unique, single, selective chemo sensor. With the current breathalyser once breath enters the device, the sensor interacts with the gas molecules producing an electrical signal. The sensor itself is composed of a catalytically active semiconductor material, based on tungsten trioxide and which specifically targets nitric oxide and ammonia in breath. In fact, the sensor was developed in 2008 and was shown to be still able to detect minute levels of nitric oxide gas in the presence of interfering volatile organic compounds.[3]

For their study, the team recruited participants, with a positive PCR test for COVID-19 and who were admitted to an intensive care unit receiving mechanical ventilation. Breath samples were collected on days 1, 3, 7 and 10 of the study or until patients no longer required mechanical ventilation.[4]

Findings

A total of 46 patients were included, 23 of whom were COVID-19 positive and the others who were all negative and served as a control group. Among the COVID-19 positive cohort, the median age was 61 years (61% male). Using the breathalyser, the authors identified three typical analytical patterns which they termed the NO-pattern, NH3/O2-pattern and the omega pattern, which was specific to patients with COVID-19 and arose from the interaction between nitric oxide, ammonia and oxygen in the exhaled samples. This omega pattern was detectable within 72 hours of the onset of respiratory failure and identified in 14 of those with confirmed COVID-19 on day 1 but only 4 of those in the control group and this difference was statistically significant ($p < 0.0001$).

Interestingly, the authors also reported on how as patients' clinical symptoms resolved, the omega pattern disappeared, and they generally transitioned to the NO pattern through the course of their illness.

The authors determined that the omega pattern had a sensitivity of 88% and a specificity of 83% for COVID-19 on day 1 and concluded that future studies are needed to determine which other diseases or infections might benefit from their technology.

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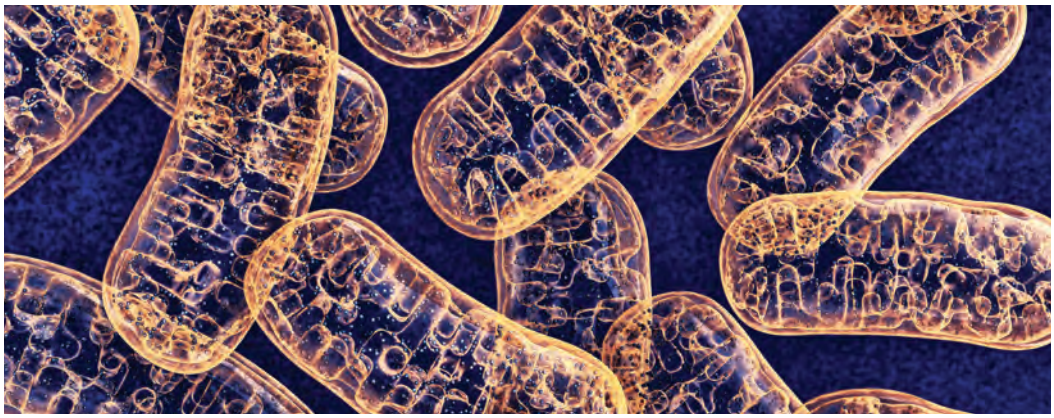
Whole genomic sequencing a useful diagnostic test for mitochondrial disorders



The use of whole genomic sequencing has been shown to increase the diagnostic yield by a third in patients with suspected mitochondrial disorders.

The use of whole genomic sequencing was found to enable a definite or probably genetic diagnosis in 31% of patients with suspected mitochondrial disorders according to a study published in the BMJ.[1]

Mitochondria are the fundamental cellular energy system in cells and disorders of the mitochondrial system can affect several organ systems that use a large amount of energy including the brain, nerves and muscles.[2] In fact, evidence suggests that such disorders are estimated to affect around 1 in 4300 adults.[3] Mitochondria have their own DNA (mtDNA) although the majority of proteins which make up the structure of mitochondria are created in the nucleus (nDNA). A mitochondrial disorder can be defined as any disorder which affects the structure of function of the mitochondria and can arise from mutations in either mtDNA or from within the nuclear genome.

Current methods for diagnosing mitochondrial diseases rely on biochemical screening of blood, urine or cerebrospinal fluid, followed by next generation sequencing of mtDNA and nDNA.[4] While sequencing the protein coding regions of all genes (or exome sequencing) can be effective at identifying mitochondrial genetic diagnoses, this approach fails to identify 40% of cases.[5]

For the present study, a team from the Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK, set out to determine whether whole genomic sequencing could define the molecular basis of suspected mitochondrial disorders. Using the 100,000 Genomes project, the team recruited patients referred for further testing and with a suspected multi-system, progressive disorder involving the central nervous system, the neuromuscular system or both. DNA samples were extracted from a blood sample and sequenced.

Findings

A total of 345 individuals with a median age of 25 (54% female) from 319 different families were included and had their whole genome sequenced. The researchers identified a definite or probable genetic diagnosis in 31% (98/319) of families. The team made a definite genetic diagnosis in 28% of families which included 14 diagnoses (4% of the 319) that provided only a partial explanation of their clinical symptoms. In total, 95 different genes were implicated and interestingly, of the 104 families given a diagnosis, only 38% were in genes known to cause a primary mitochondrial disease (6 mtDNA and 30 nDNA). The remaining 63% had a genetic diagnosis based on non-mitochondrial genes.

The authors commented on how the use of whole genome sequencing as a first-line approach to genetic testing has not been fully explored and felt that around 90% of mitochondrial disorders could be detected using this approach. They suggested that whole genome sequencing is a useful diagnostic test for those with mitochondrial diseases and which should be offered early in the diagnostic patient pathway.

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Three microRNAs could serve as a potential biomarker for cognitive decline

The presence of three microRNAs measured in blood could represent a novel, minimally invasive, approach to the identification of cognitive decline in patients according to research by a team from DZNE and the University Medical Center Göttingen (UMG), Germany. Cognitive decline is a key feature of neurodegenerative diseases and is often the first symptom experienced by patients and which develops slowly over time. However, the use of biomarkers that are elevated at the "pre-cognitive" decline stage could theoretically serve as a means of identifying those at risk of future and further decline.

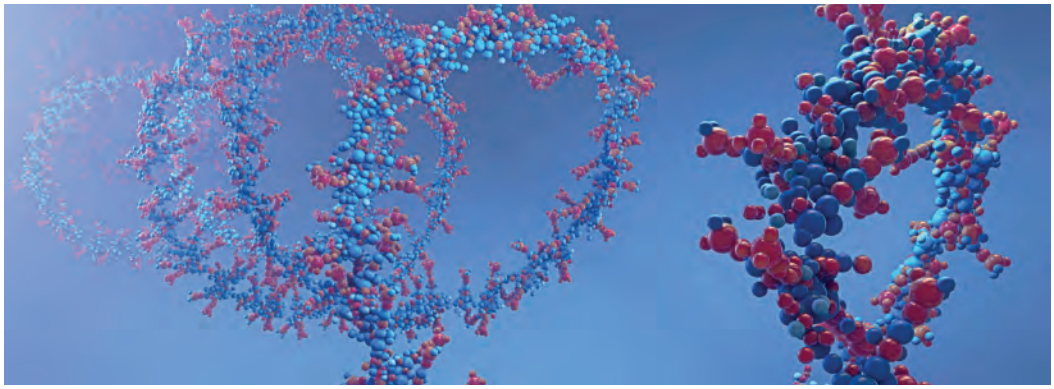
The use of biomarkers for the early detection of diseases has advanced in recent years for example in Alzheimer's disease,[1] and one area of research has focused on microRNAs, which are small (19–22 nucleotide), non-coding RNA molecules which regulate gene expression and protein homeostasis through binding with a target mRNA.[2] A further advantage of microRNAs is their stability in cell-free environments and that these have been implicated in the cause of Alzheimer's disease[3] and cognitive disturbances.[4]

For the present study,[5] the German team used a maze test as a mouse model for age-associated memory decline with both young and older animals. The results showed that the older mice displayed behaviour that was indicative of cognitive decline. When analysing blood samples, it became clear that there were elevated levels of three microRNAs that were only present in the older mice. But whether these markers were also present in humans was unclear but using blood samples from adults with mild cognitive impairment, the researchers also found a significant elevation of the same three-microRNA signature which were absent in matched healthy controls.

In an attempt to strengthen the association between the three-microRNA signature and cognitive decline, the German team used blood samples from patients in a study examining subjective cognitive decline. Interestingly, they found that patients with initial mild cognitive impairment who later developed Alzheimer's disease, had a significantly higher expression of the three-microRNA signature. Further confirmation of the importance of the microRNA signature came from an analysis of cerebral spinal fluid (CSF) of those with cognitive impairment which also demonstrated significantly higher levels, confirming that the biomarker was present in both blood and in CSF.

Because there was elevation of the three-microRNA signature, the team wondered if inhibition of the three-microRNA might reduce the degree of cognitive decline. Returning to the mice, the team injected an inhibitory mix into both older and younger mice and found that the older mice displayed an improved ability to escape the maze that was comparable to the younger animals. Finally, using a mouse disease model of Alzheimer's disease, the team also demonstrated that the inhibitory mix appeared to ameliorate memory impairment in those with the Alzheimer's disease model.

Although these were preliminary findings, the authors concluded that the screening approach 'could improve the early detection of individuals at risk for pathological cognitive decline and increase the chance for efficient therapeutic intervention'.



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