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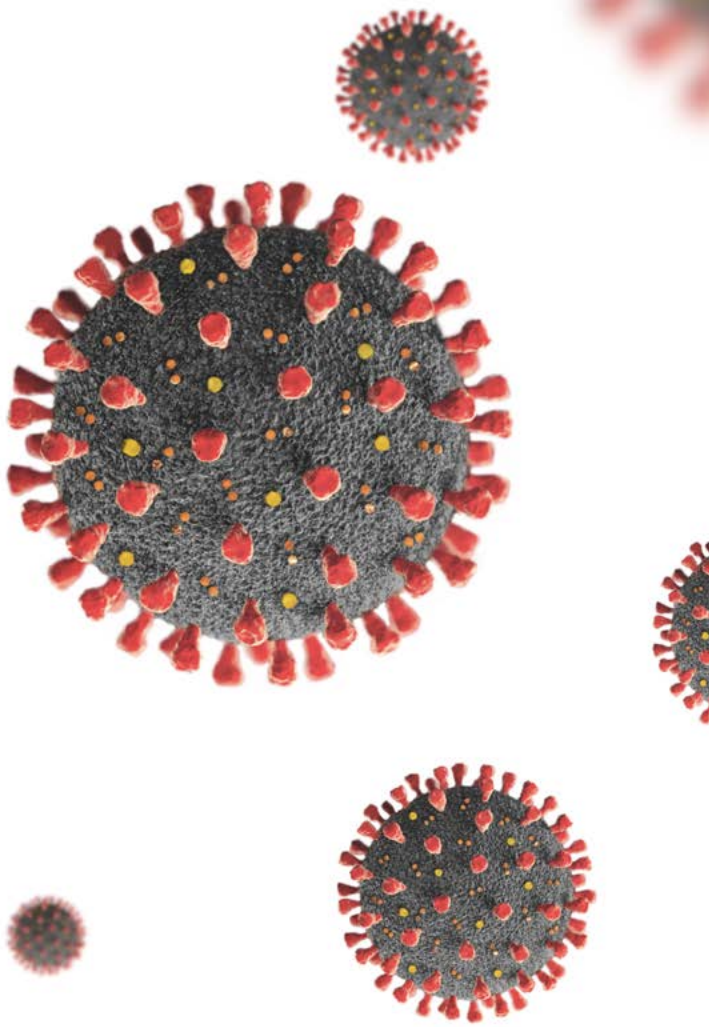


Featured articles:

- The true impact of Australia's COVID-19 lockdowns on critical health diagnoses
- Targeted approach versus genome-wide non-invasive prenatal testing
- Minor changes to androgen reference ranges

The true impact of Australia's COVID-19 lockdowns on critical health diagnoses

By Dr David Deam and Dr Simon Nazaretian

As one of Australia's largest pathology providers, Clinical Labs was amongst the first to witness pathology numbers drop by a staggering 40% in April 2020. Although many prominent figures in Australian healthcare, including the Hon. Greg Hunt MP, Minister for Health, urged Australians not to delay medical appointments, cancer screenings and pathology tests, the Australian public avoided these healthcare services, wary of exposure to the new virus.

Due to the critical role pathology plays in the management of chronic health conditions and the diagnosis of cancers, Clinical Labs became increasingly concerned about the corresponding drop in the vital diagnoses of malignancies and chronic conditions, including diabetes.

At the end of 2020, an analysis was undertaken to investigate the true impact the COVID-19 pandemic had on these critical disease diagnoses. Data from our histology and biochemistry laboratories spanning five years (Jan – Oct 2016-2020) was extracted and used to calculate the percentage of abnormal results reported during the time period.

Year-on-year test numbers allow Clinical Labs to calculate an estimate of expected referrals for any given year. These projections are used in preparing the laboratories for the coming year but are equally useful in determining the impact of the COVID pandemic on pathology referrals.

By combining Clinical Labs data and data from Medicare Australia we were able to calculate the impact of the downturn in testing for each state.

In the pages that follow we will take you through the key findings and implications of this data and share with you the true impact Australia's 2020 COVID-19 lockdowns had on critical health diagnoses.

COVID-19 pandemic impact on cancer diagnoses

It is well known pathology referrals, including histopathology referrals, fell dramatically in 2020. However, the impact on community morbidity and mortality may not have been fully appreciated. Clinical Labs has undertaken in-depth analysis of referral data to illustrate the significant impact the pandemic has had on malignancy diagnoses.

The drop in histopathology tests and cancer diagnoses in 2020

The impact of the COVID-19 pandemic and lengthy lockdown periods in Victoria throughout 2020 resulted in a significant reduction in pathology episodes and reduction in histopathology tests across the state. Our **Clinical Labs laboratories received 17.8% fewer histopathology biopsies and tests** than projected for the January to October 2020 period, and based on state Medicare data, **nearly 100,000 fewer histopathology samples were received by Victorian laboratories** than projected over this period.

This is also reflected in the reduced number of malignancies diagnosed. Clinical Labs laboratory data for the January to October 2020 period shows a **17.3% reduction in the diagnosis of more common malignancies (melanoma, breast cancer, prostate and bowel cancer and lung cancer)** than estimated, based on our positive diagnosis rates for these cancers.

The findings were similar in New South Wales, where our laboratories received 16.3% fewer histopathology samples than projected and according to Medicare data, all NSW laboratories received over 100,000 fewer samples than projected. The reduction in histopathology samples also aligned with a 16.3% reduction in the diagnosis of malignancies by our NSW anatomical pathologists.

Western Australia and South Australia were less affected by strict lockdown periods in 2020 and this is reflected in the data in the following table for these states. However, the findings still show a downturn in samples and corresponding diagnoses.

At a glance - Downturn in histopathology samples and malignancy diagnoses by state in 2020

State	Downturn in histopathology samples by state (Medicare data)	Percentage downturn in histopathology samples Clinical Labs	Percentage downturn in malignancy diagnoses Clinical Labs
VIC	98,931	17.8%	17.3%
NSW	105,831	16.3%	16.3%
WA	18,343	12.50%	12.50%
SA	7,784	9.50%	9.50%

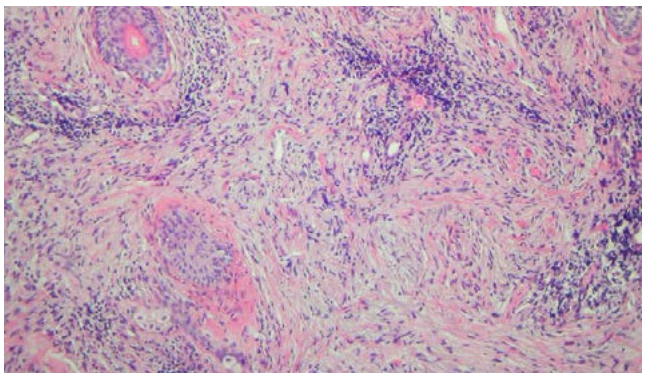
Table 1 – Estimated histopathology downturns by state Jan-Oct 2020

What does this reduction in diagnoses mean for the health of patients within our community?

From Jan to Oct 2020, it is estimated:

- Over 1000 Victorians were not diagnosed with melanoma or melanoma in situ.
- Nearly 650 breast cancers and 650 bowel/prostate cancers were not diagnosed in Victoria.
- Similarly, almost 140 Victorians were not diagnosed with lung cancer.

As of October 2020, these patients were undiagnosed and not receiving the early treatment so vital to improving prognosis of malignancy.



Estimated undiagnosed malignancies (Victoria)

Cancer Type	Number of Undiagnosed Victorians
Melanoma	853
Melanoma in situ	150
Breast Cancer	649
Prostate Cancer	283
Bowel Cancer	358
Lung Cancer	138

Table 2 – Estimated number of Victorians with undiagnosed malignancies (Jan-Oct 2020). Based on statewide Medicare data and Clinical Labs cancer diagnosis rates.

Our data analysis also estimated there to be hundreds of people in New South Wales with undiagnosed malignancies at Oct 2020, as detailed in the following table. While fewer malignancies were undiagnosed in Western Australia and South Australia, the numbers remain significant even for these less-impacted areas.

Undiagnosed malignancies (New South Wales, Western Australia and South Australia)

Cancer Type	NSW	WA	SA
Melanoma	392	46	93
Melanoma in situ	455	61	5
Breast Cancer	217	109	6
Prostate Cancer	47	18	10
Bowel Cancer	305	126	5
Lung Cancer	45	65	4

Table 3 – Estimated number of people in New South Wales, Western Australia and South Australia with undiagnosed malignancies (Jan-Oct 2020). Based on statewide Medicare data and Clinical Labs cancer diagnosis rates.

Delays in the diagnosis and treatment of these cancers may result in their progression to a later stage, associated with increased morbidity and mortality rates. Additionally, the influx of new patients requiring more aggressive surgeries and treatments may place added strain on our healthcare system.

It is vital that we all vigorously seek out the thousands of people who were not screened in 2020 to facilitate the earliest diagnosis of any malignancies.

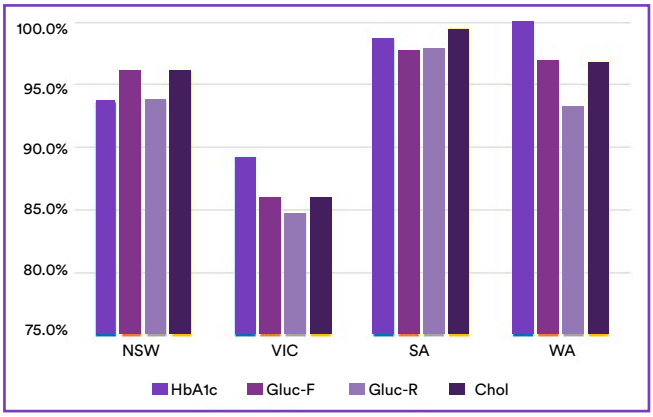
COVID-19 pandemic impact on diabetes and cholesterol testing, diagnosis and management

With the downturn in pathology referrals in 2020, Clinical Labs also saw a decline in biochemistry referrals, resulting in thousands of tests not being carried out.

The downturn in diabetes and cholesterol tests in 2020

The reduced number of samples received at our laboratories was partly due to people being locked down or reluctant to visit their doctors. Others had request slips for their routine tests, including diabetes and cholesterol, but were reluctant to attend collection centres during outbreaks.

The below graph shows the number of diabetes and cholesterol tests received in Jan to Oct 2020, as a percentage of our projected numbers.



Graph 1 – The actual number of diabetes and cholesterol tests that Clinical Labs performed in 2020 as a percentage of projected numbers. (Gluc-F = fasting glucose, Gluc-R=random glucose, Chol= cholesterol)

To put these downturns in perspective, a 1% reduction in HbA1c testing represents over 17,000 tests not being completed across Australia.

As expected, these downturns mirror the lockdowns and COVID-19 case numbers experienced in each state, with Victoria being the most affected.

The corresponding impact of the downturn in testing numbers on test results

Due to the volume of tests for diabetes and cholesterol performed each year, the number of people who may have gone undiagnosed or unmanaged for these conditions is estimated to have run into the thousands, as shown in the table below.

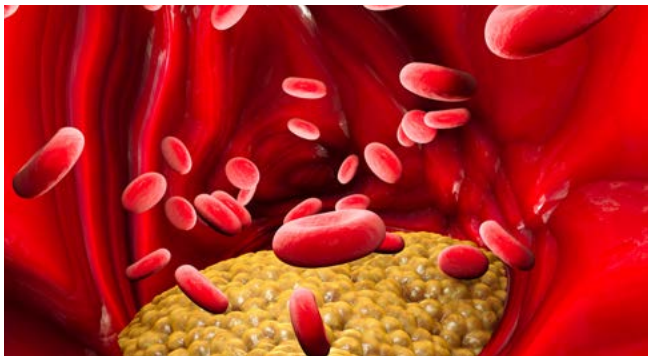
	HbA1c	Glucose (fasting and random)	Cholesterol
VIC	18,134	8,017	27,616
NSW	3,398	1,309	2,717
WA	60	457	2,032
SA	661	2,138	297
Total	22,253	11,921	32,662

Table 4 – Estimated number of unperformed tests returning an abnormal result. (Clinical Labs data Jan–Oct 2016-2020)

What does this reduction in testing mean for the health of patients within our community?

These findings indicate there were many thousands of people in 2020 who missed having tests for the diagnosis or monitoring of common morbidities.

This downturn in testing may result in poorer short- or long-term outcomes for patients, delaying or missing diagnosis and treatment of chronic conditions.



Summary

- Based on the extraction and analysis of data from our laboratories and Medicare data, it is estimated thousands of Australians should now be undergoing treatment for malignancies that may remain undiagnosed.
- In addition, thousands of Australians missed important diagnostic and monitoring tests for diabetes and cholesterol abnormalities.
- At Clinical Labs, we have seen firsthand the impact the 2020 COVID-19 pandemic had on critical health diagnoses; we want to help protect the health of Australians and do everything possible to ensure patients who missed vital testing are assessed at the earliest opportunity.

Recommendations

- It is vital to seek out and follow up on patients who missed cancer screening tests in 2020, including patients on your practice skin check recall lists, who may have missed six-monthly or annual skin checks in 2020.
- Now is a good time to send communications to patients on your diabetes recall lists, to help them get the management of their condition back on track.
- In the event there are more lockdowns during this current or future pandemics, it is important to continue reinforcing to patients the importance of attending their cancer screenings and routine blood tests, that they can attend these essential healthcare services, and should continue to do so.

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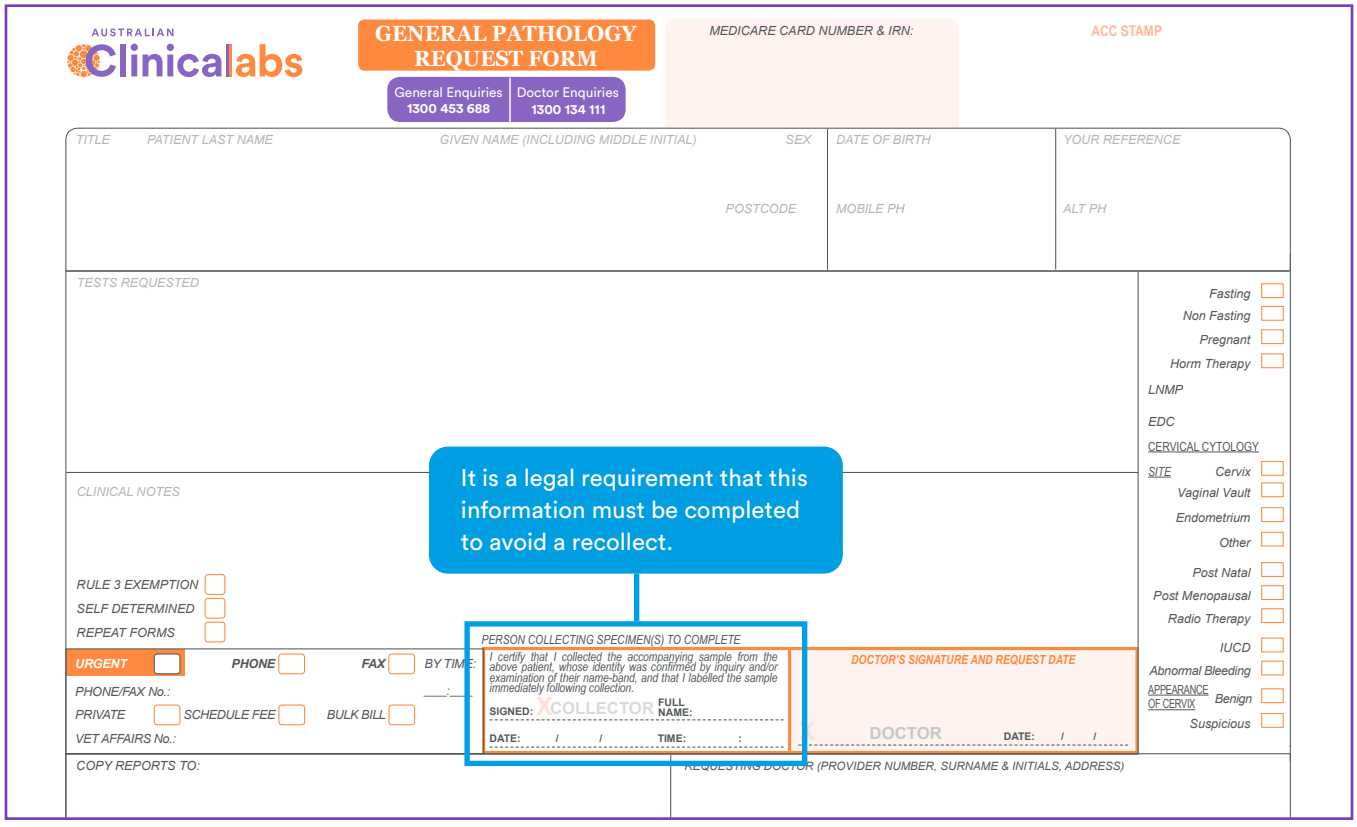
Simon graduated from Monash University in 1997 and worked as a hospital medical officer for Southern Health until 2001. Simon has been a senior lecturer with Monash University Faculty of Medicine, Nursing and Health Sciences since 2000 and Associate Investigator with Monash University Centre for Synchrotron Science since 2009. He has worked as an anatomical pathologist at The Royal Women's Hospital and Southern Health from 2008 to 2013. Simon joined Australian Clinical Labs (then Healthscope Pathology) in 2010 and further developed his interests in Gynaecological and Breast pathology, Infertility, Urology and Cytology. Simon completed his Diploma of Management in 2011. From 2011 to 2013 Simon was Coordinator of the Royal College of Pathologists of Australasia (RCPA) Victorian Anatomical Training Program and between 2013 and 2018 was RCPA Victorian State Councillor and in 2012 he received the RCPA Outstanding Teacher Award. Simon was a member of the Clinical Advisory Committee for the Commonwealth Department of Health's Digital Health Agency. In 2018 he became Clinical Director of Anatomical Pathology for Victoria and South Australia for Clinical Labs, focussing on business development and marketing. He is also a Medical Testing Assessor for NATA and is a member of the Anatomical Pathology Advisory Committee and examiner for the Royal College of Pathologists of Australasia.

Avoid patient recollects and delayed results by correctly labelling patient samples

By Associate Professor Chris Barnes

Accurate patient identification and labelling of patient specimens are critical in providing a safe laboratory and transfusion service. Our laboratories are governed by the National Association of Testing Authorities (NATA) and we are required to have detailed and robust testing procedures within our laboratories. Unfortunately, there is often less rigour applied to the "pre-analytic" phase of a sample's journey. Specimens may arrive in the laboratory with inadequate patient identification and sample labelling.

Did you know that it is an absolute (legal) requirement to provide a signed referral which includes two patient identifiers (e.g. name and dob), referring doctor's details AND a signed declaration from the person collecting the sample? Without these details, the laboratory staff are required to organise a recollection of the sample which puts the patient at significant inconvenience and delays providing results. The majority of recollections in our laboratories are as a result of "doctor collects" where the referral or the sample has not been adequately labelled. Making sure you label the sample correctly AND sign the collection declaration will allow us to get the results to you as soon as possible so you can continue caring for your patients.



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Associate Professor Chris Barnes is the National Director of Haematology and provides strategic direction nationally for haematology at Clinical Labs. He is a clinical and laboratory trained haematologist who has been part of Melbourne Haematology and has worked with Clinical Labs (and previously Healthscope) for several years. A/Prof Barnes also works at the Royal Children's Hospital and is director of the Haemophilia Treatment Centre. He has experience in both management and leadership positions. A/Prof Barnes has an active clinical research interest and is also director of Melbourne Haematology (Clinical) and Melbourne Paediatric Specialists.

Targeted approach versus genome-wide non-invasive prenatal testing

By Associate Professor Mirette Saad

Since the discovery of the fetal cell-free DNA (cfDNA) in maternal plasma, large progress has been made in the development of non-invasive prenatal screening tests.

Non-Invasive Prenatal Testing (NIPT), based on circulating free DNA, has been available in Australia since 2012. It has been broadly adopted by clinicians and patients due to its high analytical sensitivity and specificity in screening for the most common fetal autosomal aneuploidies, including Trisomy 21, 18 and 13. It can be offered to all pregnant women from 10 weeks of pregnancy onwards, in naturally conceived or in vitro fertilisation (IVF) singleton or twin pregnancies (including those with egg donors). NIPT can also be used to screen for fetal gender and, in singleton pregnancy, for sex chromosomal aneuploidies (SCAs), and, if selected, micro-deletions.

NIPT methods have capabilities and limitations along with associated challenges for diagnostic services and healthcare providers. There are currently two major cfDNA NIPT technologies: “Genome Wide (GW)” and “Targeted” detection methods.

Targeted cfDNA prenatal screening approach for the common trisomies provides the highest accuracy and sensitivity of this non-invasive screening test with a high detection rate and a very low false-positive rate (<0.1%). The test offers high analysis depth across the clinically relevant chromosome alleles within the targeted region. Focused NIPT screening approach, therefore, reduces unnecessary invasive follow-up diagnostic techniques which is the main advantage of cfDNA non-invasive screening compared to the conventional combined first trimester screening (cFTS).

On the other hand, Genome-Wide (GW) cfDNA analysis represents an enhanced screening tool for prenatal detection of chromosomal abnormalities, allowing identification of clinically relevant imbalances, that are not detectable by conventional cfDNA testing, rather than being confined to screening for the three major trisomies. The rationale for such a policy is that GW testing has the potential to identify rare autosomal trisomies (RATs) (other than 13, 18, 21 and the sex chromosomes) and rare additional fetal segmental imbalances (SIs), but, with shallow analysis depth across all chromosomes.

This article highlights some points of concern in using cfDNA GW NIPT approach for fetal aneuploidy screening.

Benefits and Limitations The basic principle of prenatal screening is to offer a safe, accessible and accurate test to all pregnant women in order to identify those women with an increased likelihood of having a baby with a chromosomal aneuploidy that can cause birth defects.

This principle seems to be applicable through targeted NIPT screening. However, so far, the benefits of GW screening for all genetic chromosomal abnormalities and imbalances do not seem to outweigh the potential harms. Therefore, clinical implementation, even in a research setting, may be questionable ethically.

Complex Counselling There are ethical and legal issues (including costs and availability) around the complexity of counselling procedures required before and after GW cfDNA NIPT regarding those rare conditions and patients’ consent for the future plan of management. For GW NIPT patients, the potential for other unanticipated findings of relevance to maternal health (including maternal genomic imbalances) should be included in pre-test counselling.

Patients undergoing a GW antenatal screening should be clearly informed of the capabilities and limitations of this test, including the possible difficult clinical decisions if positive findings of unknown significant chromosomal abnormalities were obtained.

Higher False-Positive Rates Literature shows that using GW-cfDNA analysis may fail the main goal of targeted screening method of antenatal screening. Wider, less targeted, screening results in increased false-positive findings of rare chromosomal abnormalities, resulting in an increased rate of unnecessary invasive follow-up diagnostic procedures for conditions of unknown significance.

Guidelines The HGSA/RANZCOG, along with international guidelines, recommend Down Syndrome screening in the first trimester to all pregnant women by either cFTS or cfDNA NIPT depending on local resources, patient demographics, and individual patient characteristics.

Currently, a broader GW-cfDNA NIPT approach is *not recommended by clinical guidelines* and may violate World Health Organisation (WHO) screening principles. Updated guidelines by HGSA/RANZCOG 2018, state that *“routine population-based screening for genome-wide chromosome abnormalities are not recommended due to the absence of well-performed clinical validation studies”* (HGSA/RANZCOG 2018).

This is clearly due to the uncertainty as to the clinical significance of a heterogeneous set of chromosomal abnormalities and how best to manage a positive result. Therefore, follow-up care for positive cases has not been adopted by clinical guidelines.

Updated guidelines by HGSA/RANZCOG 2018, state that "routine population-based screening for genome-wide chromosome abnormalities are not recommended due to the absence of well-performed clinical validation studies" (HGSA/RANZCOG 2018).

Higher Failure Rates and TAT While both targeted and GW-cfDNA NIPT methods have, overall, similar sensitivity, the targeted NIPT test demonstrates a significantly lower failure (no call) rate and a shorter Turn Around Time (TAT) compared to GW testing.

Targeted NIPT is the Preferred Patients' Choice
Large cohort surveys of pregnant women showed they would prefer the use of targeted over GW NIPT methods. False-positive results are always associated with inevitable anxiety that, in some cases, leads to pregnancy termination even after a normal diagnostic result is received.

In summary, it is clear that GW testing can potentially detect some additional clinically significant unbalanced chromosome abnormalities which would otherwise be undetectable except through an invasive test or, perhaps, ultrasound abnormalities. However, the implementation of genome-wide NIPT is under debate because the benefits of detecting other fetal chromosomal aberrations must be balanced against the risks of discordant positives, parental anxiety, and a potential increase in invasive diagnostic procedures. More follow-up studies on the use of genome-wide screening using cfDNA from maternal plasma is required.

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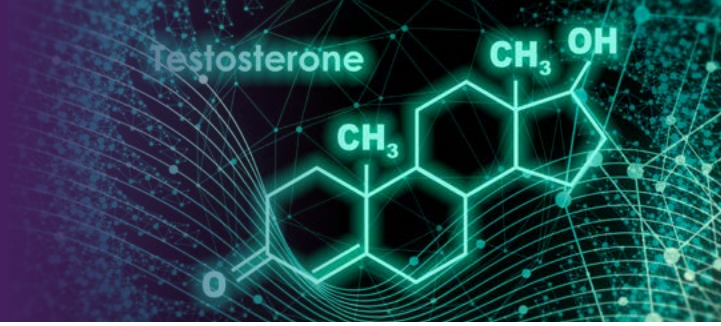
Minor changes to androgen reference ranges

By Dr David Deam



Clinical Labs knows the importance of having accurate and precise results so that informed decisions can be made about the management and treatment of patients. Part of this involves modifying assay configurations and test information as assay procedures improve.

Our supplier of testosterone reagents (Siemens) has completed a standardisation of their Testosterone II Assay. The purpose of the restandardisation is to align the assay more closely to the American Centers for Disease Control (CDC) Hormone Standardization (HoSt) Testosterone Reference Measurement Procedure. This is a program set up to assist with the accurate standardisation of various hormone assays.

The Siemens testosterone assay is designed to have a correlation coefficient of greater than 0.95 when compared to an isotope dilution-liquid chromatography-tandem mass spectrometry (ID-LC-MS/MS) testosterone method. Typical data obtained for the Siemens assay showed a level of 0.98.

This has meant some minor alterations to the reference ranges for testosterone and the derived parameters of free androgen index and free testosterone. The restandardisation impact is primarily at the low end of the assays and the effect on levels above 1.7 nmol/L is minimal.

The new references ranges will be shown on reports along with a notification of the changes.

At a Glance - Androgen Reference Ranges for Adult Female

Test	Old Range	New Range	Unit
Testosterone	0.4 - 2.1	0.3 - 1.8	nmo/L
Free Androgen Index	0.6 - 9.4	0.4 - 8.0	%
Free Testosterone	8 - 55	7 - 48	pmol/L

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