From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: FW: Repromed 1st Response [SEC=OFFICIAL]
Date: Monday, 26 October 2020 10:53:00 AM
Attachments: image002.png
image003.png
Letter to NATA Repromed_22Oct20_Interim Letter.docx

Hi [redacted] & [redacted], please find attached a letter Repromed has sent to NATA about the test. It seems that there are some concerns about how the tests was originally validated. NATA is expecting a further response tomorrow.
Regards
[redacted]

From: [redacted]
Sent: Monday, 26 October 2020 8:57 AM
To: [redacted]
Cc: [redacted]
Subject: FW: Repromed 1st Response

REMINDER : Think before you click! This email originated from outside our organisation. Only click links or open attachments if you recognise the sender and know the content is safe.

Dear [redacted] an [redacted]
Please see the initial response from Repromed regarding the cfDNA assay.
We are expecting a further response tomorrow.
Regards
[redacted]
Yours Sincerely
[redacted]
National Association of Testing Authorities, Australia

www.nata.com.au
Level 1, 2-6 Railway Parade
Camberwell, Victoria 3124
Phone: [redacted]
Fax: [redacted]

cid:image005.png@01D61DFD.AC7330D0

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21 October 2020

[redacted]
National Association of Testing Laboratories (NATA)
628 Ipswich Road
Annerley
QLD 4103

Dear [redacted]

Thank you for your letter dated the 19th of October. Please find below answers to the queries that you have raised.

Records of the incident including any immediate actions taken, investigations to establish the root cause and any subsequent follow up actions.

Monash IVF's NI PGT program was launched following an almost four-year long process of research and validation.

The research and validation, led by [redacted] focussed on whether the genetic results from NI PGT systems were as accurate as those from gold standard PGT-A with trophectoderm biopsy.

[redacted]

The validation data was obtained on a cohort of 121 embryos, and showed the two methods were very similar in their outcomes of detecting aneuploidy. There was a correlation of 98% between invasive PGT and NI-PGT; consequently the test was submitted for NATA accreditation. The NATA accreditation audit with peer review from a technical expert and review of validation report occurred in early 2019 and was ultimately approved. Monash IVF Group launched the NI PGT-A program across New South Wales, Northern Territory, Queensland, South Australia, Tasmania and Victoria in May 2019. The test has also been performed on behalf of [redacted] in [redacted]

As part of our routine surveillance program, a review of the NI-PGT outcomes was undertaken in June 2020. This review considered not only how accurately the two alternatives performed in terms of detecting abnormality, but also in clinical pregnancy rates. This review highlighted some variations of the performance of the test in clinical use, as compared to the validation results:

- Failed DNA amplification rates were pleasingly lower than the validation study (2.6% Surveillance vs 5.0% Validation).
- There was an increase in inconclusive rates compared to validation study (6.3% Surveillance vs 1.6% Validation); however both outcomes were within parameters experienced in routine clinical practice.
- **The significant unexpected finding, was that there was a significant increase in aneuploidy rates in the NI PGT tested embryos when compared to the current invasive PGT tested embryos.** This was evident across all ages and for non-delayed and delayed embryos. The increase in aneuploidy was 20-30% higher in the NI PGT group.
- **This implies that the concordance (where a conclusive genetic results was obtained) between NI-PGT and biopsy PGT is significantly less than the 98% in the validation data, and that there may be a higher false positive rate compared with PGT-A with biopsy, indicating that more embryos may have been called abnormal when in fact they may be normal, compared with biopsy PGT-A.** Although this discrepancy maybe attributed to multiple contributing factors (including that the media may be representative of more cells and maybe detecting low level mosaicism), it was evident that assessing the culture media represented ploidy status of the embryo differently to that of the cell based biopsy test (PGT-A) in our current clinical program.

The discordant results between Biopsy PGT and NI PGT prompted a full interrogation of the validation study data files to try and better understand these unexpected outcomes. **This review revealed some discrepancies in the validation data that are not yet fully understood but bring into question its scientific and clinical validity.**

A full interrogation of the validation study data files is continuing and is made more difficult by the fact that the lead investigator, [redacted] The original Laboratory notebooks have only recently been located in [redacted] personal effects and will support this process.

The following findings relating to the original validation data have been identified:

- 16 samples in the main validation study table (validation summary document) were duplicates of other samples in the same table
- 6 samples in the main validation study table (validation summary document) were triplicates of other samples in the same table
- 31 samples listed cannot be identified from any source data spreadsheet or lab book, attempts into identifying these are ongoing.
- 6 samples in a source data spreadsheet which contains the other samples are not included in the validation table and with no explanation notes. It is unclear why these samples have not been included and it could be interpreted that they may have been deliberately omitted from the validation summary table. 4 of these 6 samples show discordance between culture media and biopsy, which if included would lower the overall concordance rate.
- Additionally, investigations have revealed that the calling for the cell biopsy and media samples were not done blindly.

We are now working to conclusively identify each of these samples present in the validation summary, verify these against the sequencing data analysis platform to visually check the conclusions made regarding concordance with biopsy. We are also tracing each sample in the validation table back to the patient record to match with a biopsy and media record.

In parallel, a re-validation program has commenced. 40% of the targeted 120 samples have been collected and await unblinding. Upon the completion of re-validation, if a decision is made to re-launch the clinical offering of the test, we will discuss the accreditation requirements further with NATA. Depending on sample availability, this will likely not be completed until 2021.

Monash IVF are in the process of considering and establishing an investigation into the root cause.

Yours Sincerely

[redacted]

DRAFT