NEWSLETTER

This newsletter centers on reproductive topics with a genetics focus. If there is an organization or upcoming webinar you'd like me to include in a future newsletter, please feel free to reach out at genetics@modernreproduction.org.

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Webinars

MSRGN'S GENETICS SUMMIT 2023

A Virtual Event
to be held on
October 11-12, 2023

Register

ISSUE 15

NEWSLETTER

The little lit review

1

Non-invasive cell-free DNA-based approach for the diagnosis of clinical miscarriage: A retrospective study

Nuria Balaguer, Lorena Rodrigo, Emilia Mateu-Brull, Inmaculada Campos-Galindo, José Antonio Castellón, Nasser Al-Asmar, Carmen Rubio, Miguel Milán

This article is supposed to have the data from the validation paper of Igenomix's new niPOC test. Full disclosure - I don't have access to the full article. I just viewed their recent webinar on the test.

niPOC is a blood draw at the time of a miscarriage. The placental DNA fragments are isolated and each chromosomal pair is evaluated in order to identify if a chromosomal abnormality could be the underlying cause of the miscarriage.

This option is not yet available in the US and may be most helpful in countries with different policies on prenatal screening as it sounds similar to LabCorp's MaterniTGENOME product which is also an NIPT evaluation of every chromosome pair. However, many clinics are not routinely offering MaterniTGENOME and keep the evaluation to select chromosomal conditions, so there may still be value for patients.

The speakers emphasized the patient population that the evaluation is intended for include those who experience recurrent miscarriage and at the time of ultrasound, another miscarriage is identified.

The blood draw will need to occur before the products of conception evacuate the uterus. The niPOC can be a "just in case" evaluation because if the POC sample is not obtained or if the analysis performed on the POC fails, then the niPOC results can be used to provide some information on the pregnancy.

From the webinar, the speakers made it clear the ideal process is POC sampling with microarray analysis and niPOC is not intended as a first tier test but as a back up.

While many patients may already have had NIPT before the miscarriage, the benefit of the niPOC may be the ability to perform it earlier that 10 weeks gestation as well as being a 24 chr evaluation. Importantly, fetal fraction would need to be addressed, particularly at these earlier gestations, as well as the positive predictive value.

ISSUE 15

NEWSLETTER

The little lit review

PGT-A mosaicism based on NGS intermediate copy numbers: is it time to stop reporting them?

Gerard Campos

This article is an opinion piece, focusing on the clinical utility of PGT-A intermediate copy number reporting. The author summarizes current data which points to low level mosaics having similar reproductive potential as euploids with euploid ICMs whereas high level mosaics are identified to have potentially aneuploid inner cell masses (ICM), thus not ideal for transfer. The author cites a 57% concordance rate of TE to ICM biopsies, thus questions the clinical value of even reporting the mosaic result in the first place.

Some points made:

- Intermediate copy number (ICN) can be explained by true biological mosaicism, yet other explanations exist: amplification bias, contamination, biopsy technique, or the analysis algorithms.
- "The arbitrary severity of the criteria used to define the ranges for mosaicism (i.e., thresholds of 20–80% or 30–70%) can have a significant impact on the prevalence of mosaicism diagnosed; only by adjusting these cut-of values can result in different diagnoses using the same sample."
- In order to validate mosaicism calling, labs may mix diploid and aneuploid cell lines together in stable conditions with no variation in the quantity or quality of cells analyzed which differs from clinical embryo biopsies in which the number of intact cells is unknown and the potential addition of cellular remnants.

For a totally unofficial and small poll of healthcare providers:
Do you think there is a place for "mosaicism masking" results? The results follow as:

- One respondent said it may have a place when someone has a limited number of embryos and for ease of decision making.
- However, most respondents said they did not think there was a place for mosaicism masking. Respondents cited knowing the mosaic level can be used to rank the embryos as well as provide anticipatory guidance as one respondent stated that if a low-level mosaic is transferred, the patient may want to be aware of the possibility of a persisting mosaicism and prenatal diagnosis options.
- Two respondents stated that low level mosaicism masking (the low level would be considered as euploid) may be reasonable, but differentiating between high level and aneuploidy would be important given the reproductive potential of HLM.

For the question: do you discuss other explanations of intermediate copy number?

- It was found that for some, they discuss the mosaic result may be biological but also technical given analytical platforms used and bioinformatic analysis. However, one respondent stated the primary focus of the session is on the biological explanation. Another respondent agreed that the interpretation focuses on the biological.

The author brings up great discussion points that have circulated around. To be continued....

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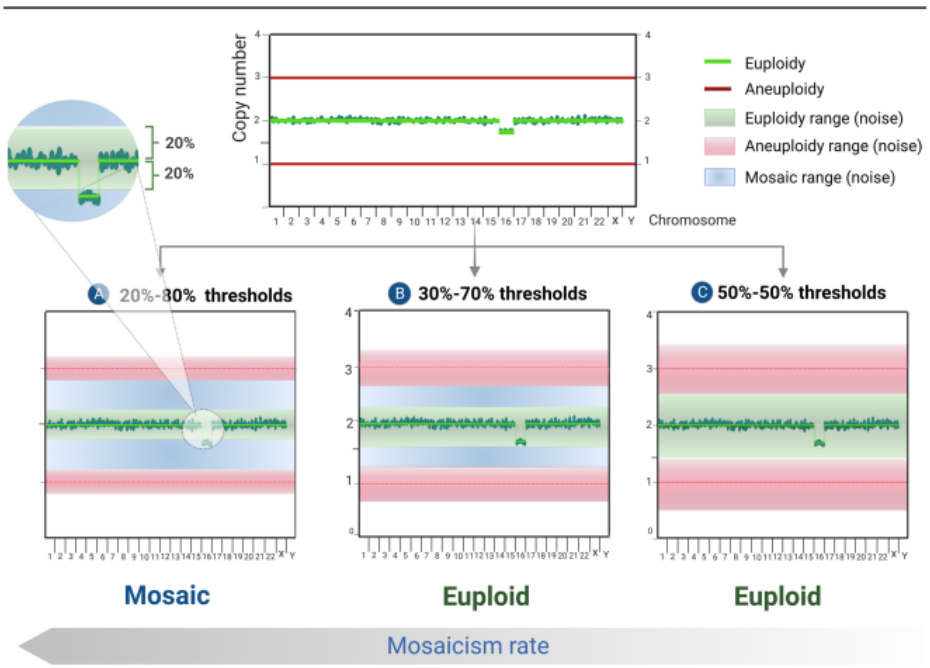

Fig. 2 Impact of thresholds on diagnosing mosaicism from NGS intermediate copy number profiles

The picture demonstrates the varying mosaicism cut offs that are used by labs compared to just a binary aneuploid/euploid cut off. I find the data plot helpful in understanding how the results are called. In discussing chromosomes with patients, I often have used the karyotype picture to explain the different chromosomal pairs, but I emphasize that technically a karyotype is not being generated for their samples, if PGT-A is ordered. Looking at these data plots, it can help make salient the cutoffs and potential for miscalling.

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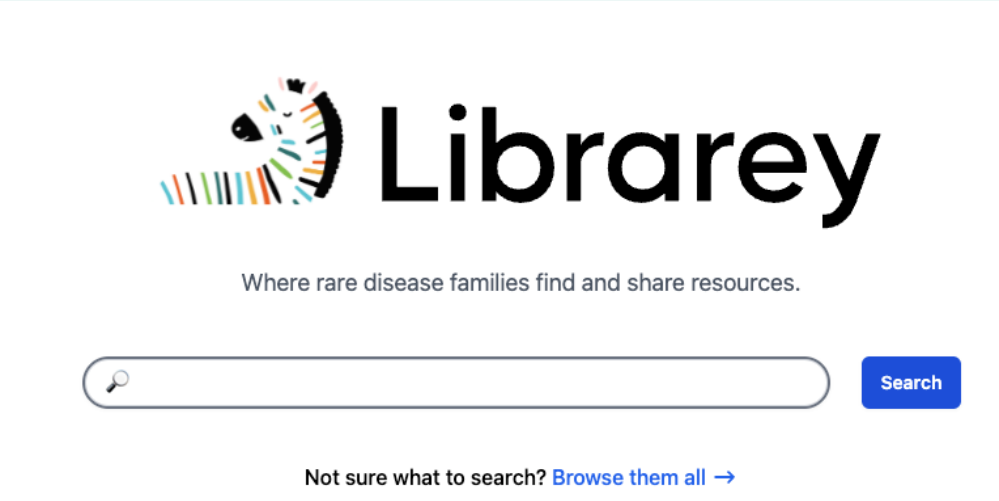
Just yes. Librarey



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