

THE ALGORITHM VALIDATION (quantusFLM® PERFORMANCE)

The validation was carried out at the Maternal-Fetal Medicine Department at Hospital Clinic Barcelona. Validation samples consisted in new cases (one image per case) recruited prospectively for the purposes of this study. Validation samples were not used for the generation of the algorithm or for other previous studies. The analysis was performed blindly and images (in DICOM format) were delineated using quantusFLM®. Only lung tissue was delineated, avoiding the heart, great vessels and surrounding areas.

	Gestational age at scan [weeks.days]		
	[28.0-39.0]	[28.0-33.6]	[34.0-39.0]
Total Samples	144	38	106
NRM %	29 (20.1%)	21 (55.3%)	8 (7.5%)
Sensitivity	86.2%	90.5%	75.0%
Specificity	86.9%	94.1%	85.7%
PPV	62.5%	95.0%	30.0%
NPV	96.2%	88.9%	97.7%
Accuracy	86.8%	92.1%	84.9%

Abbreviations

NRM = Neonatal Respiratory Morbidity

FLM = Fetal Lung Maturity

ROI = Region of Interest

PPV = Positive Predictive Value

NPV = Negative Predictive Value

References

1. Bonet-Carne et al. Quantative ultrasound texture analysis of fetal lungs to predict neonatal respiratory morbidity. UOG 2014.
2. Spong CY et al. Timing of indicated late-preterm and early-term birth. OG 2011.
3. ACOG Practice Bulletin No. 97: Fetal lung maturity. UOG 2011.
4. ACOG committee opinion no. 560: Medically indicated late-preterm and early-term deliveries. OG 2013.
5. Simon et al. National trends in primary cesarean delivery, labor attempts, and labor success, 1990-2010. AJOG 2013.
6. Towers et al. The case for amniocentesis for fetal lung maturity in late-preterm and early-term gestations. AJOG 2014.

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Quantitative ultrasound texture analysis of fetal lungs to predict neonatal respiratory morbidity¹

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INTRODUCTION

NRM (Neonatal Respiratory Morbidity), defined as respiratory distress syndrome or transient tachypnea of the newborn, is the leading cause of mortality and morbidity associated with prematurity in late-preterm and early-term births².

NRM can be caused by fetal lung immaturity. Nowadays, FLM (Fetal Lung Maturity) is mainly determined by pulmonary surfactant and it can only be assessed with laboratory tests in amniotic fluid³. These tests require an amniocentesis which is an invasive procedure.

As a consequence, the assessment of FLM has resulted in a decline in the use of this information clinically. There is an open debate about the value of FLM testing in the decision-making process for relative indications or borderline clinical situations in which late preterm or early-term delivery may seem a reasonable option but delivery could be postponed if fetal lung immaturity is assessed^{2,4-6}.

Determining the risk of FLM without the need for an invasive technique might have a tremendous impact in the clinical management of such cases. Aside from economic implications, avoiding the need of amniocentesis would be associated with less patient' discomfort and related complications, and controversies about indications for FLM assessment could be approached from a different perspective.

Transmural Biotech S.L. has developed the first automatic, non-invasive, fast and easy-to-use FLM test based on the analysis of a fetal lung image obtained by ultrasound, quantusFLM®, currently CE approved. Test can be used via Internet through a software as a service model.

KEY CONCLUSIONS

- quantusFLM® opens up the possibility of using non-invasive approaches for prenatal prediction of FLM.
- The development of this technological solution will represent a significant advance in Maternal-Fetal Medicine field.

quantusFLM®

is a non-invasive, ready-to-use clinical tool to predict neonatal respiratory morbidity through the analysis of textural features from fetal lung ultrasound images.

PRIMARY STUDY OBJECTIVE

- Demonstrate the ability of texture analysis of fetal lung ultrasound images to blindly predict the risk of neonatal respiratory morbidity.

INCLUSION CRITERIA

- Gestational age: 28+0 to 39+0
- Singleton pregnancies
- Pregnant woman who were scheduled for or at risk of delivery within 48 hours were considered eligible, including:
 - Patients scheduled for elective induction of labour
 - Patients scheduled for elective cesarean section
 - Patients with pregnancy complications, including:
 - threatened preterm labor
 - rupture of membranes
 - various pregnancy complications, mainly preeclampsia and intrauterine growth restriction
- Patients with a fetal lung ultrasound scan obtained within 48 hours of delivery
- Signed written informed consent

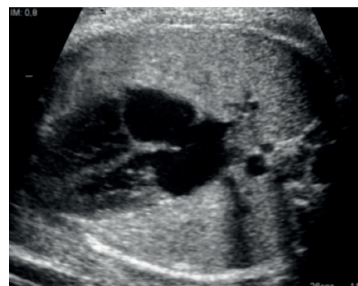
EXCLUSION CRITERIA

- Multiple pregnancies
- Fetal structural anomalies
- Chromosomal anomalies

FETAL LUNG IMAGE ACQUISITION

To perform the analysis a lateral axial transverse section of the fetal thorax at the level of the 4-chamber section of the fetal heart is required. Image inclusion criteria:

- Probe frequency: 2-6MHz
- Fetal spine located horizontally, at 3h or 9h (to avoid shadows)
- Entire thorax structure must be shown
- Avoid acoustic shadows created by bony structures
- Avoid any type of post-processing artifacts, such as: image smoothing options, Doppler measurements, calipers, pointers, speckle removing, etc.
- The use of tissue is optional but should be included if possible
- Adjustment of image settings such as gain, frequency and time-gain compensation are at the discretion of the physician performing the ultrasound

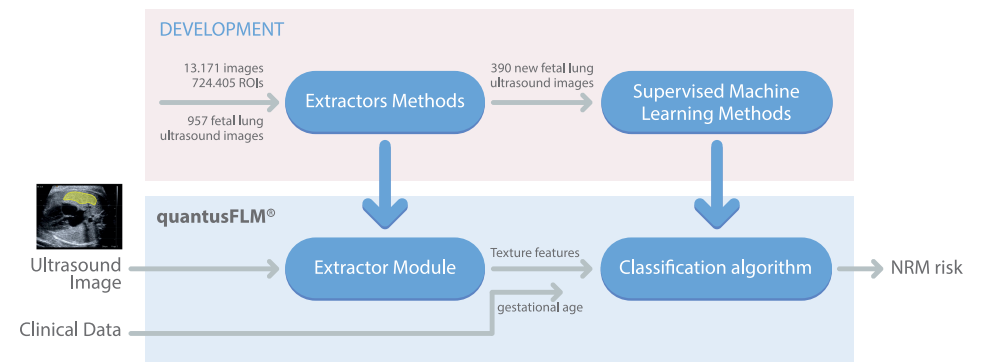


THE ALGORITHM DEVELOPMENT (quantusFLM® GENERATION)

quantusFLM® was specifically designed to be composed of two modules, a texture feature extractor and classifier.

Feature Extractor: This module is used to compact all the information contained in an image (or a region of an image) to a few features which contain relevant information. The extractor module was constructed by combining several existing mathematical methods for texture extraction in different iterations using theoretical samples. More than 10.000 images were used for illumination, rotation and resolution experiments. The feature extractor was then further refined and tuned up using 957 real fetal lung ultrasound scans. Over 7 billion computerized experiments were performed to construct the quantusFLM feature extractor module, which combines the features that demonstrated to be invariant to geometric and photometric transformations (in acquisition condition ranges).

Classifier: The classification algorithm is a sequence of various machine learning steps that combines the textural features selected (previously obtained with the extractor module) and clinical data (gestational age) to estimate the prediction of NRM risk. The parameters of this model were estimated and tuned up using 390 ultrasound images among singleton pregnancies between 24.6 and 41.6 weeks gestation.



quantusFLM® combines hundreds of textural features associated with the occurrence of neonatal morbidity. The theoretical diagnostic performance obtained was as following (Medium[95% confidence interval]):

Accuracy	Sensitivity	Specificity	PPV	NPV
87% [82-90%]	91% [77-98%]	86% [82-90%]	47% [35-59%]	98% [96-99%]