

WED-237

Advancement of artificial intelligence in digital pathology: from exploratory endpoint to primary endpoint in non-alcoholic steatohepatitis clinical trials

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Background and Aims: Improvements in liver histology is the current accepted surrogate endpoint for accelerated approval for access to treatment before the impact on clinical outcomes are known in patients with non-alcoholic steatohepatitis (NASH). Recent clinical data has demonstrated the regression of NASH as a dynamic and heterogeneous process. Depending on the effects of different disease-modifying drugs, fibrosis may regress differently, with variations in morphological and architectural features across zonal regions. Hence, a histological system developed based on changes in untreated individuals does not account well for changes after an intervention. To address this, sponsors and regulatory agencies are working to explore the use of artificial intelligence (AI) in digital pathology to facilitate accurate fibrosis assessment. qFibrosis has been used in the past in phase 2 trials to help stratify patient inclusion criteria for successful phase 3 trials. The most recent development is the US Food and Drug Administration (FDA) approving the use of qFibrosis as a primary endpoint in a NASH phase 2 study.

Method: Using a stain-free second harmonic generation and two-photon excitation fluorescence (SHG/TPE) imaging technology, qFibrosis is an AI-based tool which offers a reproducible and quantitative way to assess liver fibrosis on a continuous scale. It is a knowledge-based machine learning tool capable of automatically identifying and differentiating portal tracts and central veins, as well as to quantify collagen characteristics such as length, width, and area to provide an objective assessment on fibrosis patterns including peri-portal fibrosis, bridging fibrosis, of which these are key morphological features defined in NASH fibrosis system.

Results: qFibrosis models have demonstrated correlation with histologically determined NASH scores, with significant correlation observed for qFibrosis ($r=0.776$) whereas the correlation between central pathologists' ranges from between 0.57 to 0.81 in retrospective studies. Furthermore, qFibrosis provides additional insights such as identification of the most potent fibrosis response in baseline F3 patients in some trials. Increasingly, qFibrosis is included in prospective studies, first as exploratory endpoint to supplement analysis done by pathologists (NCT03900429), then as a secondary endpoint in a NASH phase 2b study (NCT04906421), and most recently as a primary endpoint in another phase 2 NASH study (NCT05519475).

Conclusion: qFibrosis has the potential to provide a quantitative understanding of subtle morphological changes due to treatment-induced fibrosis regression, allowing it to be more sensitive to change within the timeframes of typical phase 2 and 3 NASH trials. This can be used for better stratification of patient inclusion criteria, which is crucial for efficacy evaluation during drug development, as well as for diagnosis once the drug is approved. This clearly demonstrates the utility of AI in digital pathology in a real-world clinical setting.

Figure: NA

Advancement of artificial intelligence in digital pathology: From exploratory endpoint to primary endpoint in non-alcoholic steatohepatitis clinical trials

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INTRODUCTION

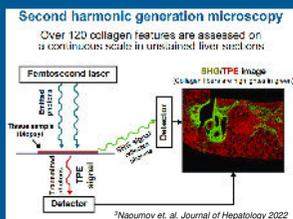
- Improvements in liver histology is the current accepted surrogate endpoint for accelerated approval for access to treatment before the impact on clinical outcomes are known in current NASH trials.
- Recent clinical data has demonstrated the regression of fibrosis in NASH as a dynamic and heterogeneous process. Depending on the effects of different disease-modifying drugs, fibrosis may regress differently, with variations in morphological and architectural features across zonal regions.
- A histological system that was developed based on changes in untreated individuals largely does not account well for changes after an intervention.
- Hence, sponsors and regulatory agencies are working to explore the use of artificial intelligence (AI) in digital pathology to facilitate accurate fibrosis assessment.

AIM

- To lead the advancement of AI in digital pathology from an exploratory endpoint to a primary endpoint in NASH clinical trials.
 - qFibrosis has been used in the past in phase 2 trials to help stratify patient inclusion criteria for successful phase 3 trials.
 - The most recent development is the use of qFibrosis as a primary endpoint in a NASH phase 2 study for the first time.

METHOD

- qFibrosis is an AI-based tool, which utilizes stain-free second harmonic generation/two-photon excitation fluorescence (SHG/TPE) microscopy to provide a standardised and reproducible quantification of NASH fibrosis on a linear scale, as well as fine details of the collagen fibres.^{1,2}
- It is a knowledge-based machine learning tool capable of automatically identifying and differentiating portal tracts and central veins, as well as to quantify collagen characteristics to provide an objective assessment on fibrosis patterns including peri-portal fibrosis, bridging fibrosis, of which these are key morphological features defined in NASH fibrosis system.



RESULTS

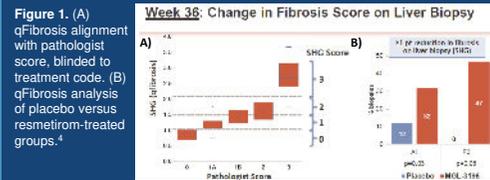
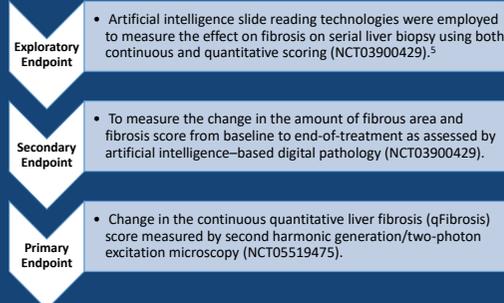


Figure 2. The advancement of qFibrosis from an exploratory endpoint to primary endpoint in NASH clinical trials



- Figure 2:** Increasingly, qFibrosis is included in prospective studies, first as exploratory endpoint to supplement analysis done by pathologists⁵ (NCT03900429), then as a secondary endpoint in a NASH phase 2b study (NCT04906421). The most recent development is reporting the change in qFibrosis as a primary endpoint in a phase 2 NASH study (NCT05519475).

- Figure 1A):** In Resmetrom phase 2 NASH study (NCT02912260), qFibrosis demonstrated correlation with pathologist's scores ($r=0.776$).
- Figure 1B):** Using SHG in a blinded retrospective study, resmetrom group showed a statistically significant ≥ 1 point reduction in fibrosis score at Week 36 in 32% of the patients compared with 12% of the patients in placebo ($p=0.03$). Furthermore, it identified patients with F3 fibrosis is the best responders.⁴
- qFibrosis has been applied in over a dozen non-cirrhotic and cirrhotic NASH retrospective studies, where correlation with central pathologists' ranges from 0.57 – 0.81. (Data not shown)

Table 1. Mean percentage agreement and linearly weighted Kappa results for inter- and intra-observer unassisted and assisted reads of liver fibrosis scoring in NASH patients.⁶

		Unassisted	Assisted
Inter-observer	Mean Percentage Agreement	89.4%	92.9%
	Mean Weighted Kappa (Linear)	0.72	0.82
Intra-observer	Mean Percentage Agreement	92.1%	96.5%
	Mean Weighted Kappa (Linear)	0.79	0.91

- SHG/TPE with qFibrosis has several advantages over standard histology for fibrosis assessment, as it removes inherent tissue-staining variations and enables the quantification of fibrillar characteristics of collagen fibers as markers of fibrosis progression and regression.
- Table 1:** The "assisted" pathologist reads, in which pathologists are provided qFibrosis information and SHG images, have been demonstrated to substantially improve inter-reader agreement of fibrosis staging with reported mean kappa values of 0.82 (i.e., near perfect agreement).⁶
- Hence, in addition to endpoints, qFibrosis has been leveraged upon to assist the pathologists in determining study eligibility based on liver disease inclusion criteria and categorical histology endpoints (NCT05519475).

CONCLUSIONS

- qFibrosis has the potential to provide a quantitative understanding of subtle morphological changes due to treatment-induced fibrosis regression, allowing it to be more sensitive to change within the timeframes of typical phase 2 and 3 NASH drug trials.
- This can be used for better stratification of patient inclusion criteria, which is crucial for efficacy evaluation during drug development, as well as for diagnosis once the drug is approved.
- Clinical relevance of qFibrosis measurements in the context of NASH will have to be established in future studies in relation to liver-related clinical outcomes.

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qFibrosis in relation to liver-related clinical outcomes

Figure 3. The ability of four selected fibrosis-related parameters (q-FPs) to discriminate between fibrosis stages 0-4 in an independent NASH cohort.⁷

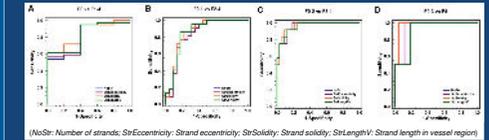
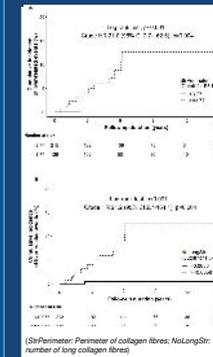


Figure 4. Incidence of liver-related events in patients stratified by q-FPs.



- Figure 3:** q-FPs has been shown to correlate with histological scoring and it provides an accurate reproducible method to evaluate fibrosis in NASH along a quantitative and continuous scale with the discriminative ability to differentiate fibrosis stages 0 – 4.
- Figure 4:** The stratification was based on the cut offs for the diagnosis of F3–F4 disease, where the values in the upper end may have additional prognostic significance, i.e., patients with high q-FPs had increased incidence of liver-related events.
- Previous longitudinal studies have shown a close association between fibrosis stage and liver-related morbidity and mortality.
- Hence, the eventual goal is to apply qFibrosis directly to predict hard endpoints in patients with NASH, as opposed to rely on ordinal fibrosis scores as a surrogate.⁹ Validation study is ongoing.

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