Automated Reflex Testing for AAT Deficiency in Liver Dysfunction: is it Worth it?

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Introduction

• Patients with low serum alpha-1 antitrypsin concentration (AAT) and specific phenotypes may have a modified risk of developing liver disease (PiMZ) and/or an increased risk of developing fibrosis and liver cancer (PiSZ and PiZZ).[1]

• The population prevalence of these phenotypes is ~3.33% (MZ), 0.2% (SZ) and 0.05% (ZZ).[1]

• Guidelines recommend an aetiological liver screen, of which AAT is a constituent, for all patients with abnormal liver function tests (LFTs).[2]

• Intelligent LFT (iLFT) is an automated aetiological screen that is performed on patients in primary care with abnormal LFTs in NHS Tayside.[3]

Aim

1) Audit the change in frequency and efficacy of testing for AAT deficiency, for 5 years prior and after iLFT was introduced.
2) Evaluate the effectiveness of our current AAT concentration cut-off for phenotyping.
3) Compare the impact of reflexing AAT measurement based on elevated liver enzymes vs. suspicion of fibrosis.
4) Estimate the financial cost of previous, current, and potential future testing strategies to diagnose AAT deficiency.

Method

• All AAT and phenotype results in adult patients (18 or older) between August 2013 and July 2023 were extracted from the NHS Tayside laboratory database and grouped by requesting indication (iLFT vs. routine clinical care (RCC)).

• iLFT automatically reflexes an AAT, among other tests, when ALT >30 U/L, ALP >200 U/L and/or GGT >73 U/L.

• Phenotyping is automatically added-on where AAT is <1.0 g/L, regardless of whether the request is iLFT or RCC.

• Fibrosis-4 indices (FIB-4), Non-Alcoholic Fatty Liver Disease Fibrosis Score (NFS), and AST-to-Platelet Ratio Indices (APRI) from iLFT patients were evaluated using age specific cut-offs; FIB-4: ≥1.3 (18 - 64) or ≥2.0 (65 and above); NFS: ≥-1.455 (18 - 64) or ≥0.12 (65 and above); APRI >0.7 (all ages).

• AAT concentrations were analysed on the Siemens Atellica platform at a cost of £3.05 per test. Phenotyping was performed by NHS Lothian, at a total cost of £10.60 (£1.83 for repeat AAT measurement and £8.77 for phenotyping).

Results

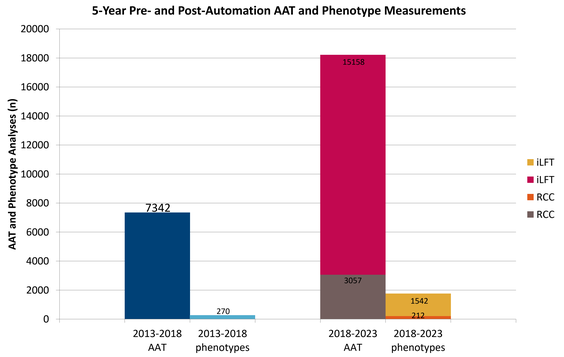


Figure 1. *Total number of AAT measurements and phenotypes performed in the 5 years before, and after, automated testing with iLFT was introduced.*

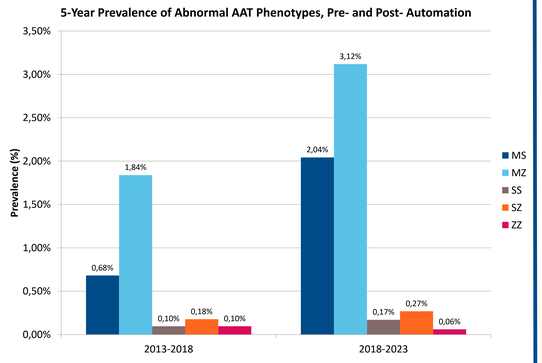


Figure 2. *Prevalence of abnormal phenotypes amongst those tested for AAT deficiency in the 5 years before, and after, automated testing with iLFT was introduced.*

• Introduction of automated testing has led to 148% and 550% increases in the number of AAT and phenotypes analysed, respectively.

• Post-automation, the prevalence of detected PiMS and PiMZ phenotypes has significantly increased, but for PiZZ has decreased (Chi-square p <0.05).

• Since iLFT was introduced, we are now detecting PiMZ, PiSZ, and PiZZ closer to their reported population prevalence.

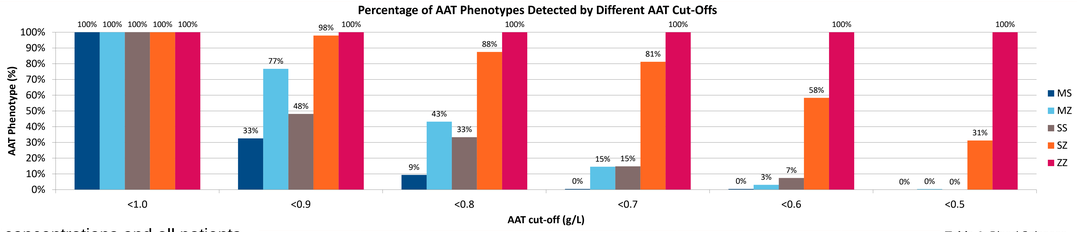


Figure 3. *Abnormal phenotypes detected at different AAT cut-offs over the 5 years post-iLFT introduction as a percentage of all detected at an AAT of <1 g/L.*

• PiZZ have very low AAT concentrations and all patients with levels <0.5 g/L would be detected if phenotyped.

• Conversely, a minority of PiMZ and PiSZ phenotypes would be missed if phenotyping thresholds are further lowered from 1 g/L.

• ALT, ALP, and GGT are poor discriminators of AAT deficiency and abnormal phenotype when compared to a primary care population suspected of having liver disease (Mann-Whitney U tests p >0.05).

• Likewise, there were no significant differences between blood-based, non-invasive fibrosis scores in those with abnormal phenotypes, compared to the general iLFT population (Chi-Square tests p >0.05).

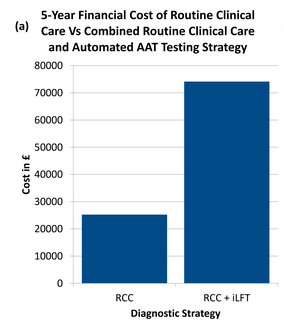
• At £25,255 vs. £74,148, five years of iLFT + RCC have cost almost three times as much as five years of only RCC.

• Reflexing AAT measurement for all patients with elevated liver enzymes but restricting phenotyping to those with very low AAT would save £16,229 (26%) and 1531 phenotypes.

• A FIB-4 based approach would lead to the largest cost and test savings (£52,110, 11,740 AAT, and 1538 phenotypes), but also the largest number of diagnoses missed.

	MM	MS	MZ	SS	SZ	ZZ	ALL
N	626 (56)	338 (34)	477 (91)	30 (1)	35 (14)	6 (5)	15158 (3057)
AAT (g/L)	1.08	0.97	0.83	0.92	0.56	0.2	1.34
ALT (U/L)	55	53	56	53	57	58	55
ALP (U/L)	78	80	87	81	101	134	91
GGT (U/L)	52	43	53	42	51	47	62
+ve FIB-4 (%)	13.4	13.2	17.3	10	22.9	50	22.5
+ve NFS (%)	19.3	18	17.4	26.7	17.6	33.3	23.5
+ve APRI (%)	5	6.3	9	3.3	5.7	33.3	12.3

Table 1. *Blood Sciences summary data from the first 5 years of iLFT, in brackets are number of phenotypes detected through RCC testing. AAT and liver enzymes are displayed as median. Non-invasive fibrosis scores show percent elevated for each phenotype. Age-specific cut-offs used for FIB-4 and NFS: FIB-4: ≥1.3 (18 - 64) or ≥2.0 (65 and above); NFS: ≥-1.455 (18 - 64) or ≥0.12 (65 and above); APRI >0.7 (all ages).*



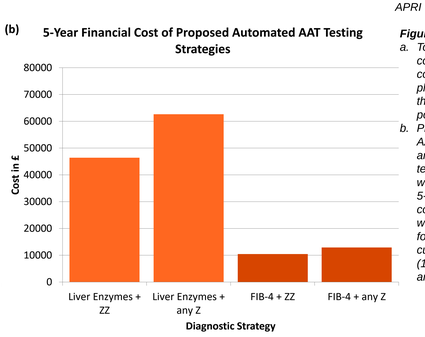


Figure 4.
a. Total 5-year financial cost of AAT concentration and phenotype testing for the 5 years pre- and post- iLFT,
b. Proposed automated AAT concentration and phenotype testing strategies with associated total 5-year financial costs. FIB-4 strategy would utilise following age-specific cut-offs: FIB-4: ≥1.3 (18 - 64) or ≥2.0 (65 and above)

Conclusions

• Automated AAT testing identifies pathological AAT phenotypes at proportions in keeping with prevalence studies and has the potential to increase or decrease test burden and costs, depending on the diagnostic strategy employed.

• Strict AAT cut-offs can be used without the risk of missing severe deficiency PiZZ phenotypes. However, more liberal cut-offs would be needed to avoid missing any PiSZ and PiMZ.

• Routinely checked liver enzyme levels don't correlate with AAT deficiency severity and/or phenotype. The same applies to relatively cheap and widely available non-invasive, blood-based fibrosis scores.

• **iLFT offers the opportunity to identify patients with significant AAT deficiency, and we have demonstrated that strategies to identify patients using non-invasive fibrosis markers result in missing significant numbers of pathogenic phenotypes. Cost-efficiency can be improved by applying lower AAT concentration thresholds for phenotyping patients. With novel therapies on the horizon, healthcare providers need to balance the cost of testing with the clinical utility of diagnosing AAT deficiency when deciding who and how to test.**

References

[1] Fromme, Malin et al. "Alpha-1 antitrypsin deficiency: A re-surfacing adult liver disorder." *Journal of hepatology* vol. 76,4 (2022): 946-958. doi:10.1016/j.jhep.2021.11.022
[2] Newsome, Philip N et al. "Guidelines on the management of abnormal liver blood tests." *Gut* vol. 67,1 (2018): 6-19. doi:10.1136/gutjnl-2017-314924
[3] Dillon, John F et al. "Intelligent liver function testing (iLFT): A trial of automated diagnosis and staging of liver disease in primary care." *Journal of hepatology* vol. 71,4 (2019): 699-706. doi:10.1016/j.jhep.2019.05.033

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