Getting the most out of Liver Blood Tests

Clinical Learning F2

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Declaration of Financial Interests or Relationships

I do not have any financial interest(s) or relationship(s) to disclose with regard to the subject matter of this presentation.
Getting the most out of liver blood tests

Why is liver disease important to us as GPs?
How do liver blood tests fit into this?
When should we be requesting liver blood tests?
Should we be relying on liver blood tests to rule out liver disease?

Innovative ways to get the most out of liver blood tests in primary care
(professor Dillon)
Why is liver disease relevant to us in primary care?

- 70% presents when cirrhosis established
- Preventable
- Asymptomatic
- Known risk factors
- Effective treatments and brief interventions
GPs current experiences are very variable..........

- Liver disease is not prioritised or incentivised at CCG or national level
- Diagnosis and referral pathways are non-existent or unclear
- Find liver blood test interpretation difficult
- Worried about missing ‘silent disease’
- Education in the field of liver disease lacking
- Feel under pressure to reduce referrals
- Feel little point in diagnosing patients as feel little available to help them
- Feel there is still a stigma around alcohol and liver disease

RCGP announces Liver Disease as a clinical priority

Publication date: 01 June 2016

THE LANCET

Health Policy | Volume 389, Issue 10081, Pages 2053-2080, May 20, 2017

New metrics for the Lancet Standing Commission on Liver Disease in the UK

Prof Roger Williams, MD • Prof Graeme Alexander, MD • Richard Aspinall, MBChB • Joanne Bosanquet, MSc • Ginette Camps-Walsh, CIM • Prof Matthew Cramp, MD • et al. Show authors

DOI: https://doi.org/10.1016/S0140-6736(16)32234-6

https://rgcpportal.force.com/s/lt-event?site=a0d0Y00000AeOP6QAN&id=a1U1n00000G7OEFEA3
Figure 1: Standardised UK mortality rate data
Data were normalised to 100% in 1970, and subsequent trends plotted using the software Statistical Package for the Social Sciences. Data are from the WHO-HFA database. Analysed by Nick Sheron (September, 2013).
Premature mortality – liver disease set to become the top cause
How do liver blood tests fit into this/what’s new?

• Little evidence that leads to a liver diagnosis out of context
• Reasons to do: risk factors for/suspicion of liver disease, symptoms or signs of cirrhosis, monitoring of drugs

CONTEXT IS KING

• Level of abnormality not a good indicator of severity
• Most will remain abnormal if risk factors remain

INVESTIGATE ALL ABNORMALITIES WITHOUT RE-TESTING – MAKE A DIAGNOSIS

• It is common for those with ALD, NAFLD and viral hepatitis (the big 3!) to have NORMAL liver blood tests
• Think of abnormal liver blood tests as one of the risk factors

DO NOT RELY ON LFTs TO RULE OUT LIVER DISEASE IN THOSE WITH RISK FACTORS
You may have noticed……

Liver Blood Tests **NOT** Liver Function Tests

Small but important difference:

Most of routine panel telling us about increased cell turnover/damage in hepatocytes (ALT, AST) and bile ducts (ALP, GGT) **NOT** telling us about function

Liver **FUNCTIONs**:
• Haem breakdown – **Bilirubin**
• Plasma proteins – **Albumin**
• Clotting factors - **PT/INR**
• Portal system – **platelets, Na**
New National guidelines emphasizing above and in line with NICE NAFLD and cirrhosis guidelines

https://vimeo.com/261822350

Re-assess risk periodically (2-5 years depending on clinical risk)

NAFLD suggested by Ultrasound and/or Negative liver screen

Determine risk of Advanced Fibrosis

Calculate FIB4 or NAFLD fibrosis score

\[
\begin{array}{c|c|c}
\text{FIB-4*} & \text{NFS*} \\
\hline
\leq 1.30 & \text{1.30 to 3.25} & > 3.25 \\
\leq -1.455 & -1.455 to 0.675 & > 0.675 \\
\end{array}
\]

Low Risk of Advanced Fibrosis

\[\leq 9.5 \text{ OR } \leq 7.8 \text{kPa}\]

ELF test OR ARFI elastography / FibroScan

High Risk of Advanced Fibrosis

\[> 9.5 \text{ OR } > 7.8 \text{kPa or invalid scan}\]

Manage in Primary Care

- Assess cardiovascular risk
- QRISK2 & Consider Statin
- Diabetes/Alcohol/Hypertension
- Weight loss

Refer to Hepatology Clinic

- For assessment of liver disease
- For management of advanced fibrosis
- Screening and treatment of Portal Hypertension
- HCC screening and management

* Higher cut-offs, <2.0 and <0.12, should be used for patients aged over 65 years.
Fibroscan (US elastography) – measures velocity of sound waves and converts into stiffness (KPa)

ELF (Enhanced Liver Fibrosis) - combines 3 serum biomarkers of fibrosis:
- Hyaluronic acid (HA)
- Procollagen III amino terminal peptide (PIIINP)
- Tissue inhibitor of metalloproteinase 1 (TIMP-1)
NAFLD screening in high risk groups? – diabetes, metabolic syndrome

Not currently recommended by NICE or BSG

BUT ....
We know many with risk factors will have normal LFTs and may still have significant liver fibrosis if investigated

Nottingham Scarred Liver project pilot:
• Fibroscan on 211 diabetics (based on RF alone not on LFTs)
• 30% had either fibrosis (Kpa >8) or cirrhosis
• 72% of those with fibrosis had ‘normal’ LFTs
• 90% of those with cirrhosis had ‘normal’ LFTs
Which method to detect fibrosis?

McPherson et al GUT 2010;59:1265-1269
Transient elastography = fibroscan

1.1.3 Offer transient elastography to diagnose cirrhosis for:

- people with hepatitis C virus infection
- men who drink over 50 units of alcohol per week and women who drink over 35 units of alcohol per week and have done so for several months
- people diagnosed with alcohol-related liver disease.
Key questions when looking at a set of abnormal blood tests:

**WHY** are the bloods abnormal? - diagnosis

**HOW SEVERE** is the liver disease? - staging
Aiming for parity with other chronic disease management:

- Design and set up templates to diagnose and assess patients at risk of liver disease
- Ensure coding is accurate and comprehensive
- Set up recalls to reassess fibrosis in these patients at regular time intervals
- Refer to alcohol, obesity and other lifestyle services routinely
Work within agreed guidelines with reference to liver related NICE quality statements:

**Quality statements**

**Statement 1** People with non-alcoholic fatty liver disease are given advice on physical activity, diet and alcohol.

**Statement 2** People with non-alcoholic fatty liver disease are offered regular testing for advanced liver fibrosis.

**Statement 3** Young people and adults with risk factors for cirrhosis are offered non-invasive testing for cirrhosis.

**Statement 4** Adults with cirrhosis are offered 6-monthly surveillance for hepatocellular carcinoma.

**Statement 5** Young people and adults with cirrhosis and upper gastrointestinal bleeding are given prophylactic intravenous antibiotics at presentation.
Be inspired by examples of local change:

Wales: Andrew.yeoman@wales.nhs.uk

Nottingham scarred liver: https://www.scarredliverproject.org.uk/

Southampton commissioned pathway: meadmathews@nhs.net

Birmingham alcohol fibrosan: andrew.holt@birmingham.ac.uk

Tayside iLFTs: j.f.dillon@Dundee.ac.uk
Now available: comprehensive web-based toolkit for all primary care professionals hosted by the RCGP

• Links to guidance
• In depth articles on all major causes of liver disease
• Best practice examples – e.g. Southampton, Nottingham
• Comprehensive list of recommended read codes to improve audit/research
• Sections for patients, nurses and commissioners

http://www.rcgp.org.uk/liverdisease
Love Your Liver

- Objectives of the campaign:
  - Raise awareness of risk factors
  - Improve early diagnosis
  - Prevent liver disease
- Simple ‘3 Steps’ message:
  - Reduce alcohol consumption
  - Improve diet & exercise
  - Reduce risk of contracting viral Hepatitis

www.britishlivertrust.org.uk
Love Your Liver

Online screener:
www.britishlivertrust.org.uk/screener

Love Your Liver – FREE resources:
www.britishlivertrust.org.uk/our-work/love-your-liver/love-liver-materials-order-form/

British Liver Trust:
loveyourliver@britishlivertrust.org.uk
iLFT-intelligent management of abnormal LFTs

Prof John F Dillon
University of Dundee
The Size of the Problem

ELDIT 1989-1997

- 1,065,570 enzyme tests, 588,416 albumin and bilirubin tests
- 12-17% of tests abnormal
- 6000 patients had a single abnormal test and no subsequent action
- Only 10% of abnormal tests explained by existing liver disease

ALFIE population

- All patients in Tayside with LFTs 1989-2007
- Incident LFTs 310,511 patients
- Incident LFT taken in primary care without obvious liver disease
- 95,977 patients
- 21.7% had at least one abnormal test
- 1.3% developed liver disease
- Median FU 3.7 years
LFT algorithms, Staging, this, that and all

“everybody in a box”
• Complex flow diagrams
• Sequential testing
• Not everybody fits
• Everybody see’s a specialist

“Its fibrosis stupid”
• Chronic liver disease is the only thing that matters
• Do a fibrosis test
  • But performance of test is diagnosis specific
  • Stable door paradigm
So what actually is the problem with LFTs?

1. Ignoring or losing the result
2. “the 42 moment” what was the question
3. Its complicated and relatively rare
4. There are too many of them
The Current Pathway

• GP decides to check LFTs on a patient’s blood
• The result is returned and in 20% of cases will be abnormal
• The GP can then decide to:
  • ignore the result
  • arrange to see the patient
• If the patient- agrees -attends,
  • repeat of the LFTs and the whole process repeated again
  • Or GP will arrange a series of blood tests to look for causes of liver disease +/- ultrasound of the liver.
• Further cycles of repeats with additional appointments and staff time for venepuncture
• At any stage the GP could also refer the patient to secondary care
• GP-patient contact and variation and loss from system
  • Average of 6 contacts
  • Less than 50% have proper follow up

10/10/2018
SOLUTION PART 1

• A working group consensus on minimum diagnostic criteria for liver diseases

• Liver disease diagnosis
  • specific, exclusive diagnostic criteria
    • Not all with the disease
    • Designed to fail safe
  • diagnosis using a minimal set of parameters
    • a high index of confidence in the positive diagnosis.
    • Therefore not including everyone

• These criteria allow patients to be allocated to one of 3 groups:
  1. Those that have serious or complex disease that requires secondary care management
     • Auto-immune liver disease, HCV, HBV
     • NAFLD with high non invasive fibrosis scores (NAFLDf score)
     • ALD with high non invasive fibrosis scores (FIB4)
  2. Those that have less serious disease that can be managed within primary care
     • Life style interventions
     • Alcohol Brief intervention
  3. Those in whom the diagnosis is not clear
     • Fail safe mechanism – think of non liver disease if not refer for specialist opinion

10/10/2018
Solution Fibrosis Markers 2

• Previously developed for cirrhosis detection
  • Poor positive predictive value, not high enough sensitivity, for poor specificity
  • Alcohol effect
  • Good negative prediction
  • Routine analytes
  • FIB 4, APRI and others

• So we can exclude fibrosis remotely, Fail safe criteria

• NAFLD fibrosis score, staging and prognosis

• ELF New analytes
SOLUTION PART 3

- Technological developments within blood science laboratories have led to the use of tracked analysers where patient samples are passed between analysers using micro rail systems, which are computer controlled.

- It can use clinical information to add to biochemical data, to generate a diagnosis as a result and email a management plan.

- Test ordering and communicating systems-ICE
iLFT Pathway

• GP requests iLFTs in ICE, adds data
  • alcohol consumption, BMI and risk of metabolic syndrome/insulin resistance.
• In the laboratory if LFTs abnormal
  • aetiological tests performed
  • staging algorithms calculated.
  • The diagnostic criteria are used to give a diagnosis
• Diagnosis in ICE results to GP and linked to management plan
  • ranging from management in general practice to referral for secondary care, 31 plans in total.

This system will deliver earlier identification of treatable liver disease, reduced GP consultations and increased management in primary care, using the smarter application of existing knowledge and technology.
A pilot evaluation of a synergistic liver diagnostic pathway: Making sense of LFTs for patients, GPs and the NHS in Scotland.

Intelligent Liver Function Testing (-iLFT)

a trial comparing the current pathway of care to one utilising the new semi-automated system
ICE Screenshots - Initial ICE screen
ICE Screenshot – BMI, Alcohol, Metabolic Sy or Insulin Resistance

Now 14 units for men and women
<table>
<thead>
<tr>
<th>Hepatic Diagnosis by GP</th>
<th>Intervention type</th>
<th>Control</th>
<th>%</th>
<th>iLFT</th>
<th>n=</th>
<th>%</th>
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<tr>
<td>ALD unspecified</td>
<td>n=</td>
<td>30</td>
<td>6.1</td>
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<tr>
<td>ALD with fibrosis</td>
<td>n=</td>
<td>0</td>
<td>0.0</td>
<td>5</td>
<td>7.8</td>
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<tr>
<td>ALD without fibrosis</td>
<td>n=</td>
<td>0</td>
<td>0.0</td>
<td>5</td>
<td>7.8</td>
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<tr>
<td>Abnormal secondary to biliary disease</td>
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<td>15</td>
<td>3.1</td>
<td>5</td>
<td>7.8</td>
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<tr>
<td>Abnormal secondary to systemic disease</td>
<td>n=</td>
<td>42</td>
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<td>7</td>
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<td>Acute hepatitis</td>
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<td>3</td>
<td>0.6</td>
<td>1</td>
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<td>DILI</td>
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<td>Gilbert’s Syndrome</td>
<td>n=</td>
<td>5</td>
<td>1.0</td>
<td>1</td>
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<tr>
<td>HBV</td>
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<td>1</td>
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<tr>
<td>HCC</td>
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<tr>
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<tr>
<td>NAFLD with fibrosis</td>
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<td>1</td>
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<td>3</td>
<td>4.7</td>
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<tr>
<td>NAFLD without fibrosis</td>
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<tr>
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<td>3</td>
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<tr>
<td>Primary Biliary Cholangitis</td>
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<td>Normalised-no diagnosis</td>
<td>n=</td>
<td>81</td>
<td>16.5</td>
<td>1</td>
<td>1.6</td>
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<tr>
<td>Not normalised-no diagnosis</td>
<td>n=</td>
<td>72</td>
<td>14.7</td>
<td>20</td>
<td>31.3</td>
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</tbody>
</table>
Change in final outcome

Final outcome in Control Group
- Hepato-biliary diagnosis: 44%
- Abnormal secondary to systemic disease: 16%
- Normalised-no diagnosis: 15%
- Not normalised- no diagnosis: 16%
- Not re-checked-not investigated: 9%

Final outcome in iLFT intervention group
- Hepato-biliary diagnosis: 56%
- Abnormal secondary to systemic disease: 31%
- Normalised-no diagnosis: 2%
- Not normalised- no diagnosis: 11%
- Not re-checked-not investigated: 0%
## Cost effectiveness

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Within trial outcome</th>
<th>Lifetime model outcomes</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Within trial</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean cost (CI 95%)</td>
<td>Probability of correct</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diagnosis (CI 95%)</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>£185</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>iLFT</strong></td>
<td>£328</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td>£146 (±63, ±228)</td>
<td>0.51 (±0.43, ±0.59)</td>
</tr>
<tr>
<td><strong>ICER</strong></td>
<td>£284 (±128, ±440)</td>
<td></td>
</tr>
</tbody>
</table>
intelligent Liver Function Testing Pathway

• GP requests iLFTs
  • alcohol, BMI and MS.
• In the laboratory if LFTs abnormal
  • Automatically
    • aetiological tests performed
    • staging algorithms calculated.
    • The diagnostic criteria are used to give a diagnosis
• Diagnosis to GP with management plan
  • 31 plans in total.

• System delivers high quality investigation to **100%** of patients
• With diagnostic accuracy over 90%
• >80% reduction in GP contacts
• 75% reduction in need to refer to secondary care
• Delivering earlier identification of treatable liver disease,
• Using the smarter application of existing knowledge and technology.
• System now Live for the whole of NHS Tayside