Chronic Liver Disease – A Taster Menu

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Consultant Hepatologist and Transplant Physician

The Liver Unit

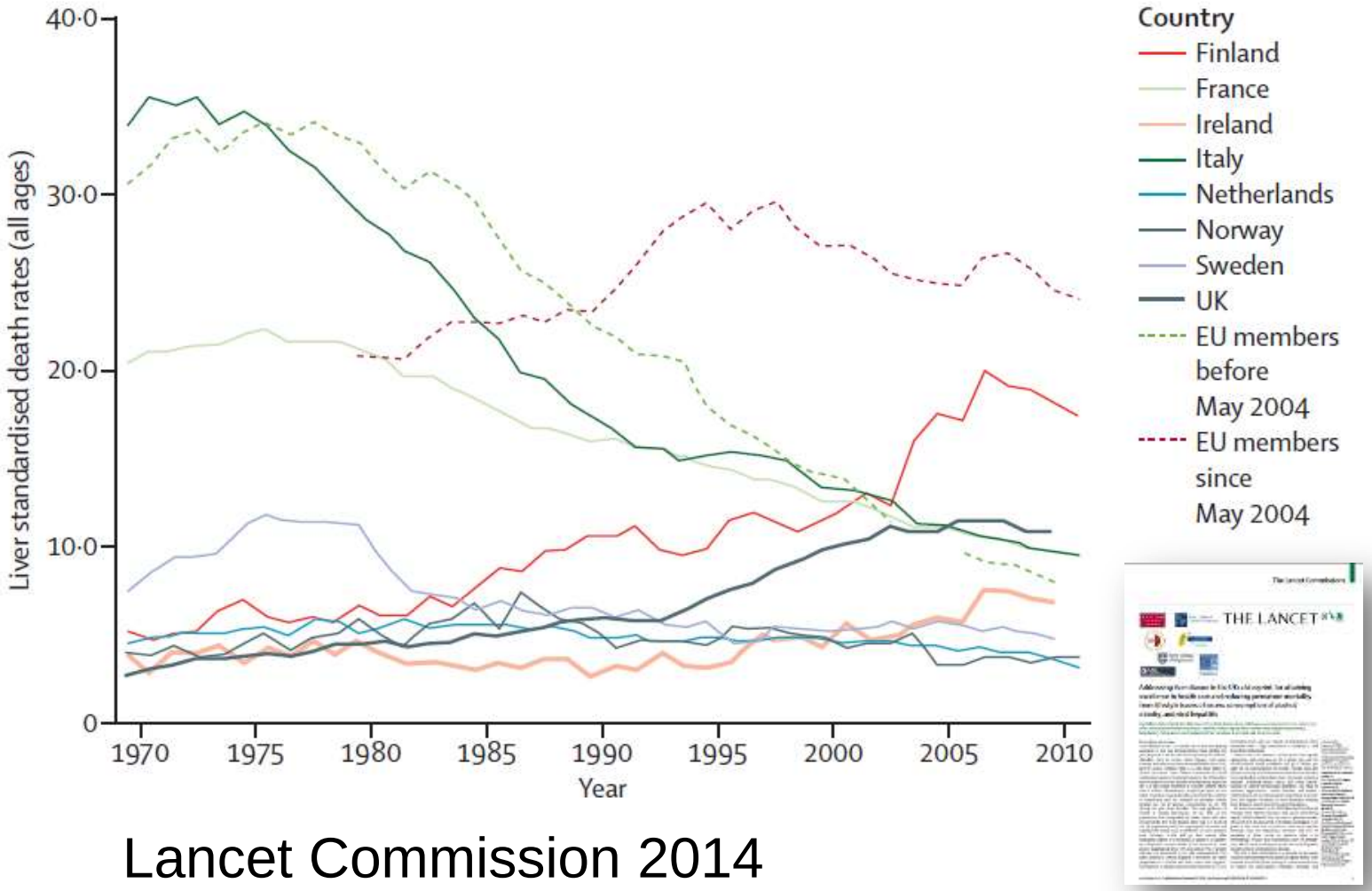
QEHB

A Drinking Song

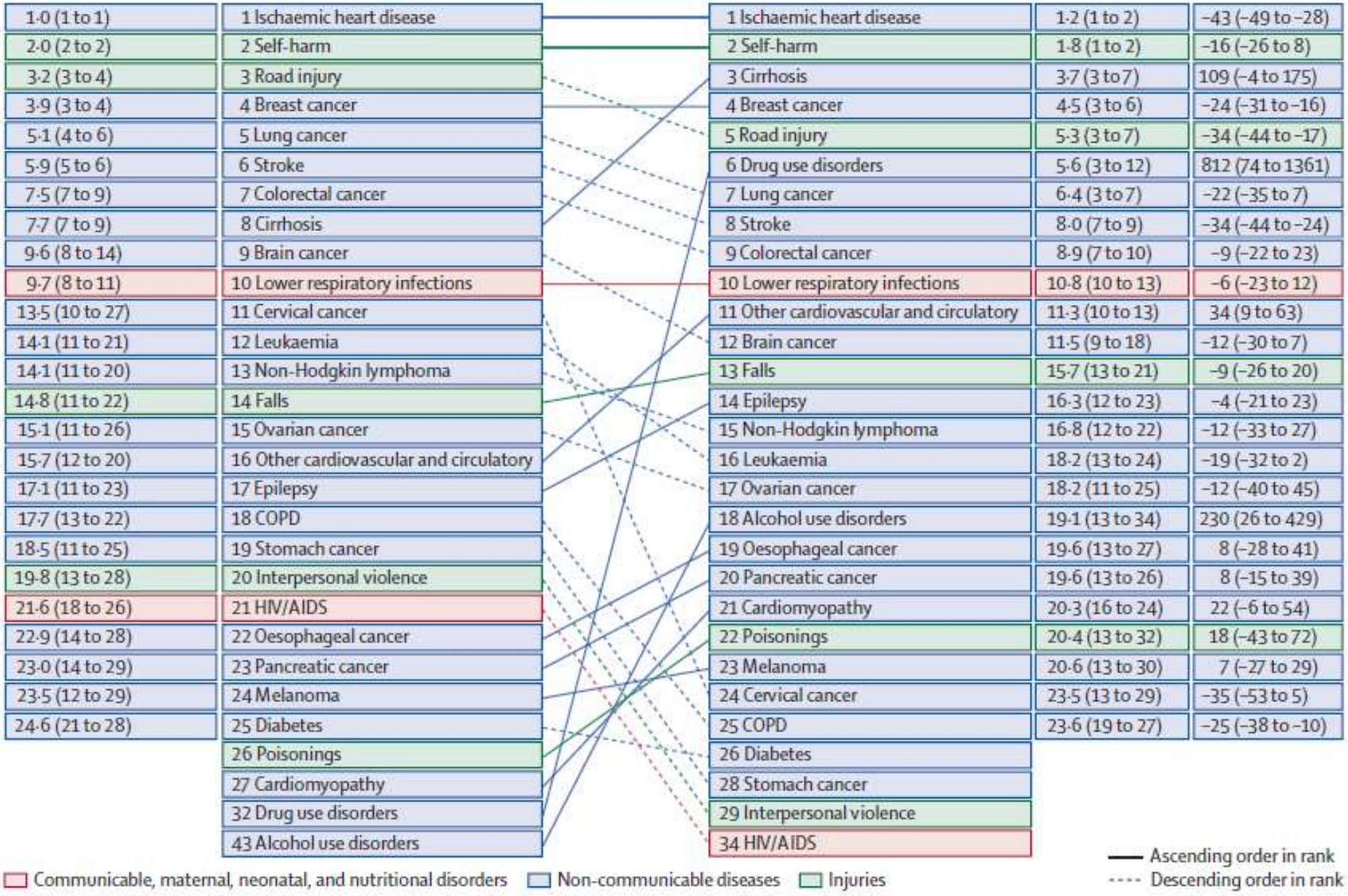
Wine comes in at the mouth
And love comes in at the eye;
That's all we shall know for truth
Before we grow old and die.
I lift the glass to my mouth,
I look at you, and I sigh.

-W. B. Yeats

The entrée



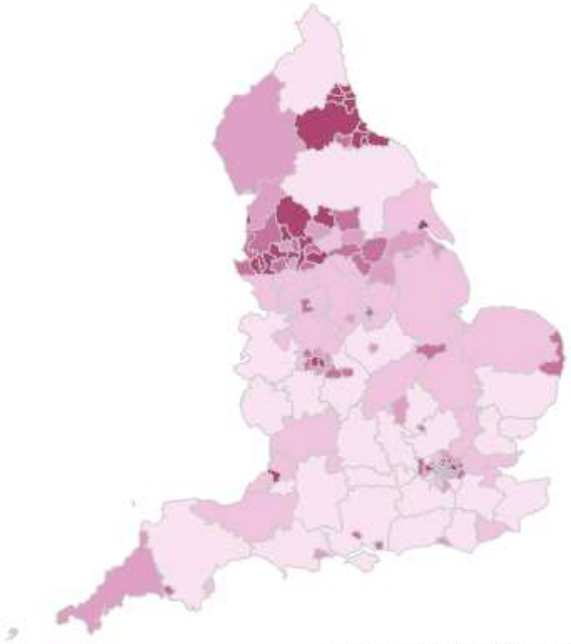
Lancet Commission 2014

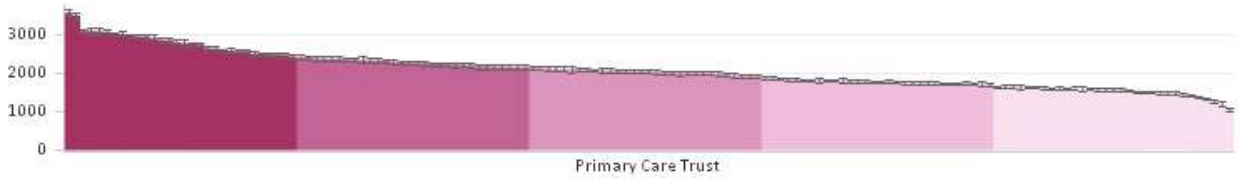


Murray et al Lancet 2013

Alcohol related admissions: all ages

Rate of alcohol related admissions per 100,000 population, by PCT, 2011/12





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- Lowest value
- Highest value

Area name	Value
Middlesbrough	3,557
Salford	3,480
Manchester Teaching	3,084
South Tyneside	3,083
Blackburn with Darwen Teachi...	3,076
North Tyneside	3,061
Liverpool	3,013
Heart of Birmingham Teaching	3,011
Sunderland Teaching	2,959
Blackpool	2,943
Newcastle	2,943
Knowsley	2,903
Redcar and Cleveland	2,848
Ashton, Leigh and Wigan	2,841
Hull Teaching	2,788
Hartlepool	2,763

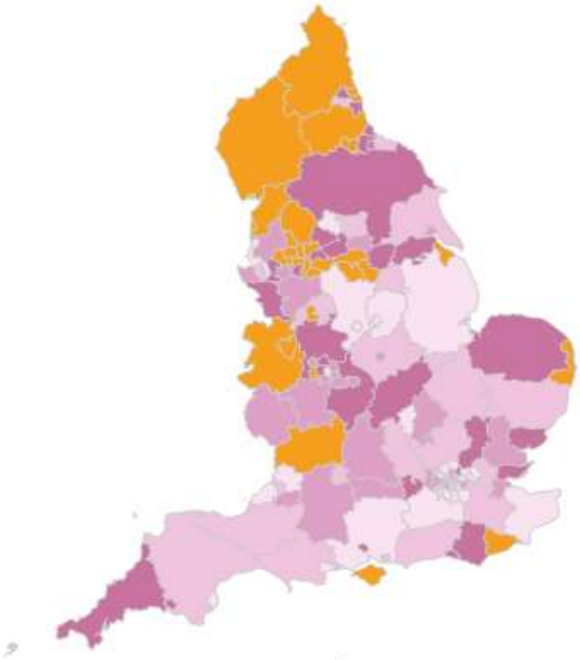
www.sepho.org.uk/extras/maps/NHSatlasLiver/atlas.html

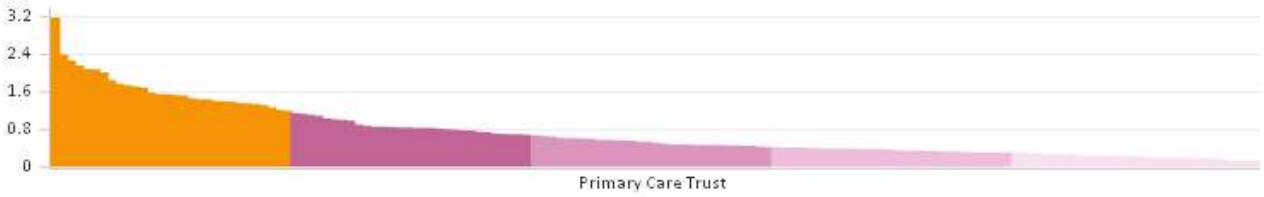
Prescription of drugs for alcohol addiction

Annual Dose Equivalent per 100,000 population, by PCT,: 2006/7 - 2010/11

RightCare

SPH Solutions for Public Health





Metadata | Help

- Not Applicable
- Lowest value
- Highest value

Area name	Value
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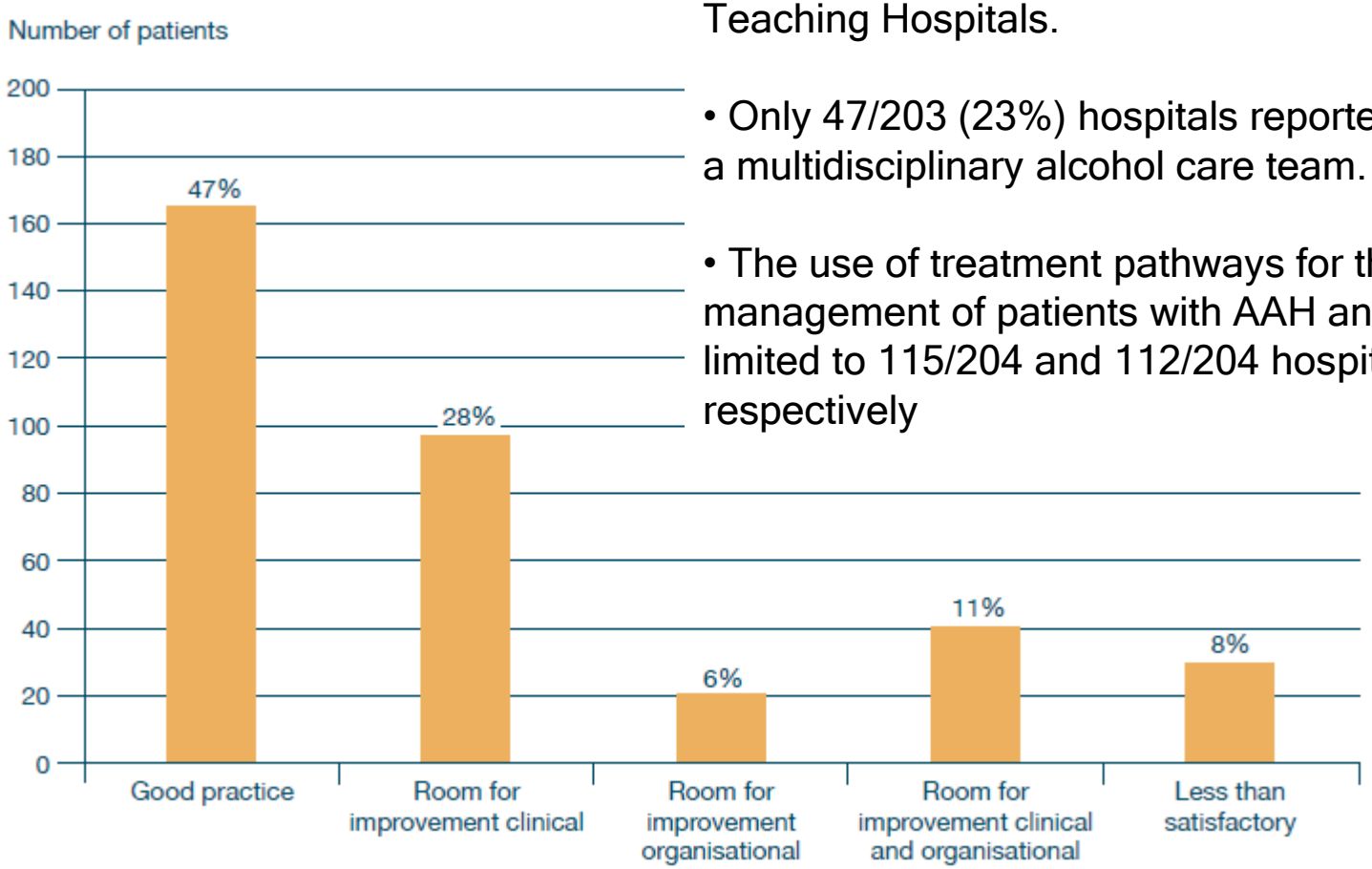
Trafford	1.14
Newcastle	1.127
Western Cheshire	1.103
Northamptonshire Teaching	1.082
Oldham	1.024
Sandwell	1.005
Brighton and Hove City	0.995
Kirklees	0.984
Middlesbrough	0.9
Hartlepool	0.874
Warwickshire	0.853
East Sussex Downs and Weald	0.849
Calderdale	0.844
Southampton City	0.838
Cornwall and Isles Of Scilly	0.837

www.sepho.org.uk/extras/maps/NHSatlasLiver/atlas.html

• Consultant Hepatologists restricted to 52/191 (28%) hospitals, 34 of which were University Teaching Hospitals.

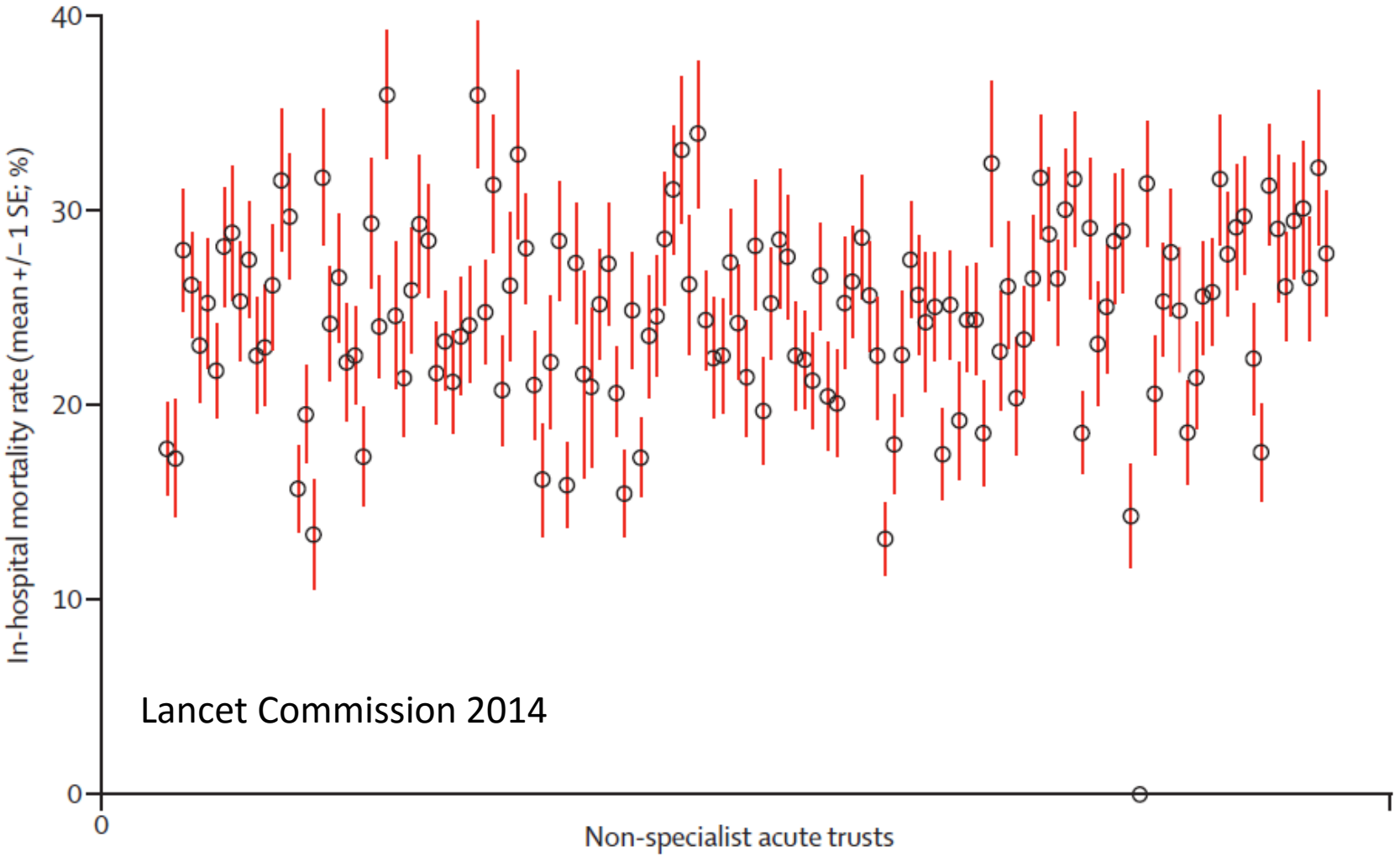
• Only 47/203 (23%) hospitals reported having a multidisciplinary alcohol care team.

• The use of treatment pathways for the management of patients with AAH and/or ArLD limited to 115/204 and 112/204 hospitals respectively



NCEPOD

There is huge variation in the UK in outcomes in liver disease



Lancet Commission 2014

At risk drinkers in Birmingham

Population 1.1 million

Increasing Risk Drinkers	130,000
Higher Risk Drinkers	44,000
Dependent	38,000

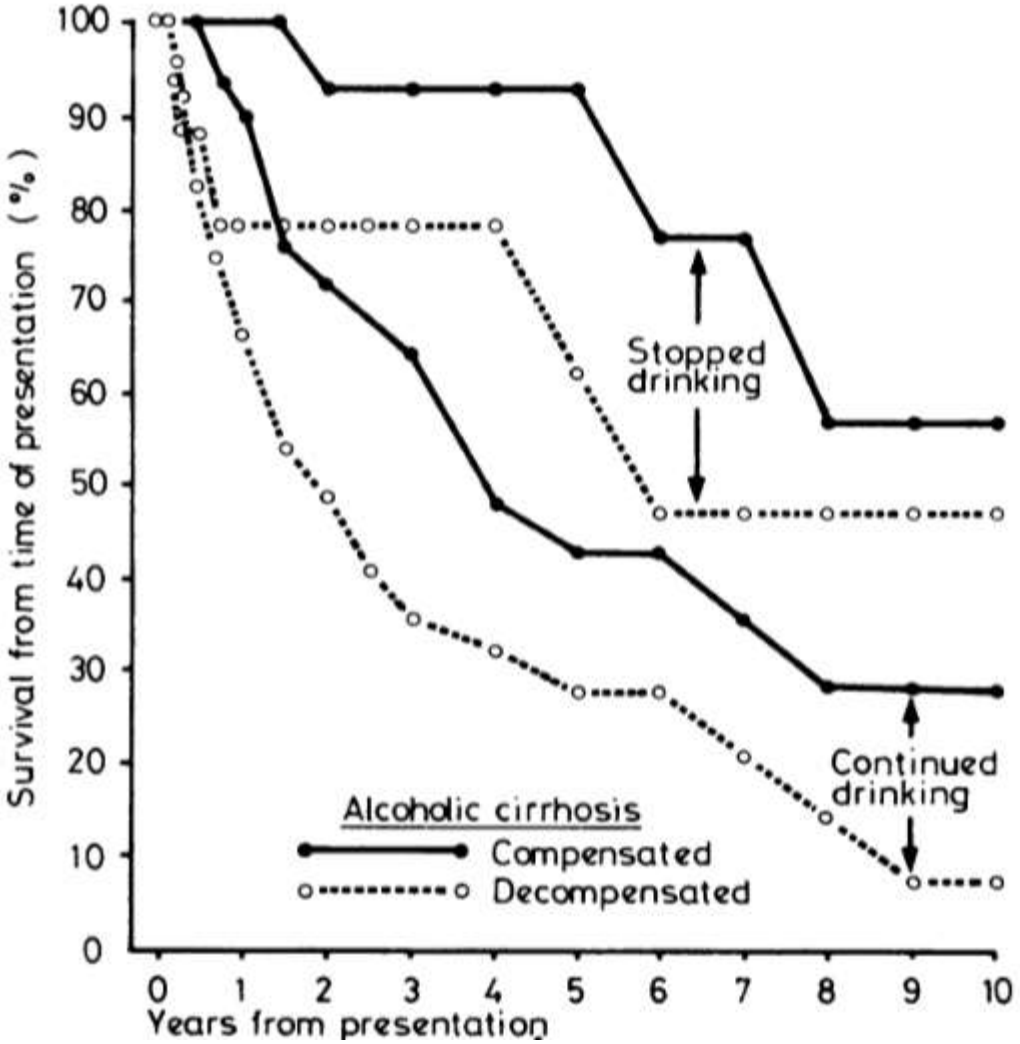
…but only 13% are in treatment

Department of Health Feb 2011

- 1.4 million pensioners drink excessively
- In England during 2010 there were more admissions for >65ys with alcohol related conditions than in 16-24yr olds
- 1:3 alcoholics develop their drinking habit in later life

A 20-year prospective study of cirrhosis.

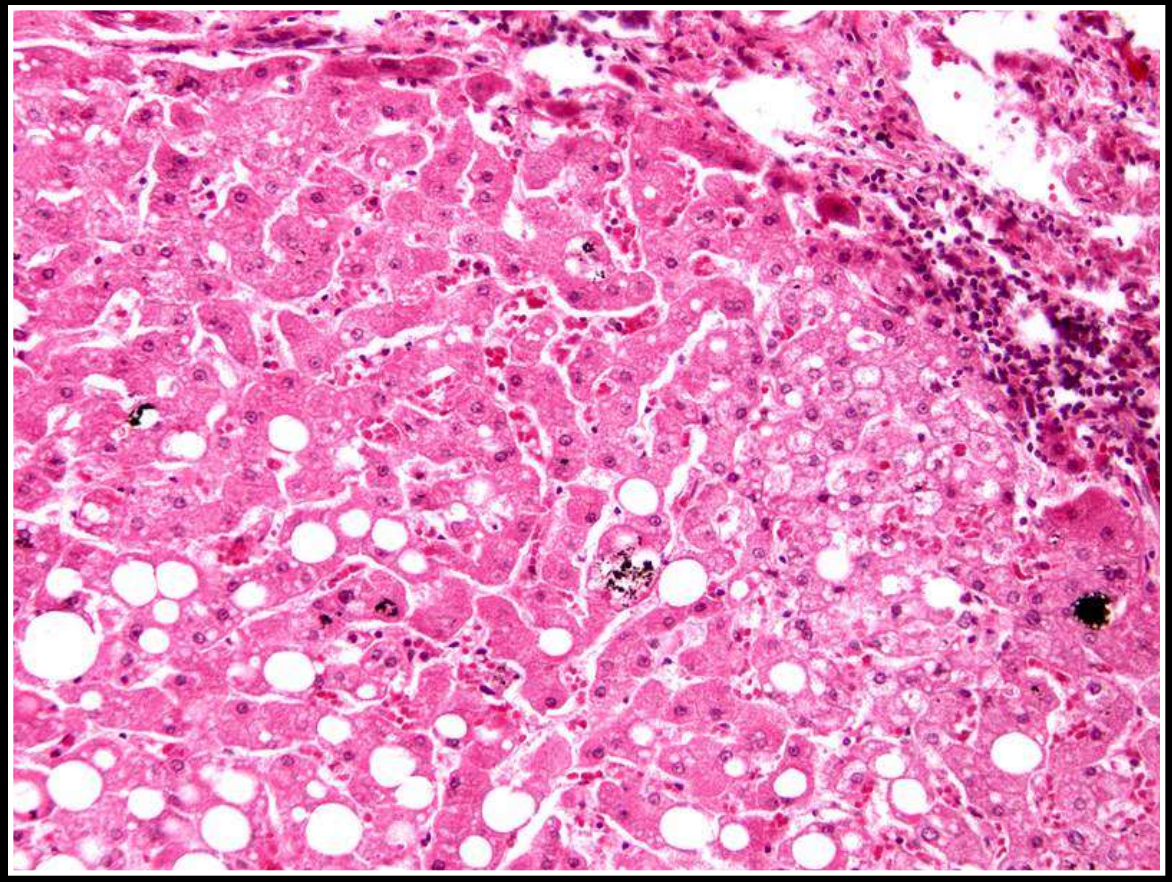
Saunders JB, Walters JR, Davies AP, Paton A



Br Med J (Clin Res Ed). 1981 Jan 24;282(6260):263-6

Lucien Freud 1995

Alcoholic disease of the liver - Mallory F BJHH 1911;22:69



Fatty Change
Inflammatory Infiltrate
Degenerative/Apoptotic Hepatocytes - DAMPs
FIBROSIS

Obesity and Dietary Fat – a benign association?

Steatosis is a characteristic feature of ALD

1) Risk of cirrhosis and HCC increased by diets high in fat(1) and CHO(2) which promote inflammation(3)

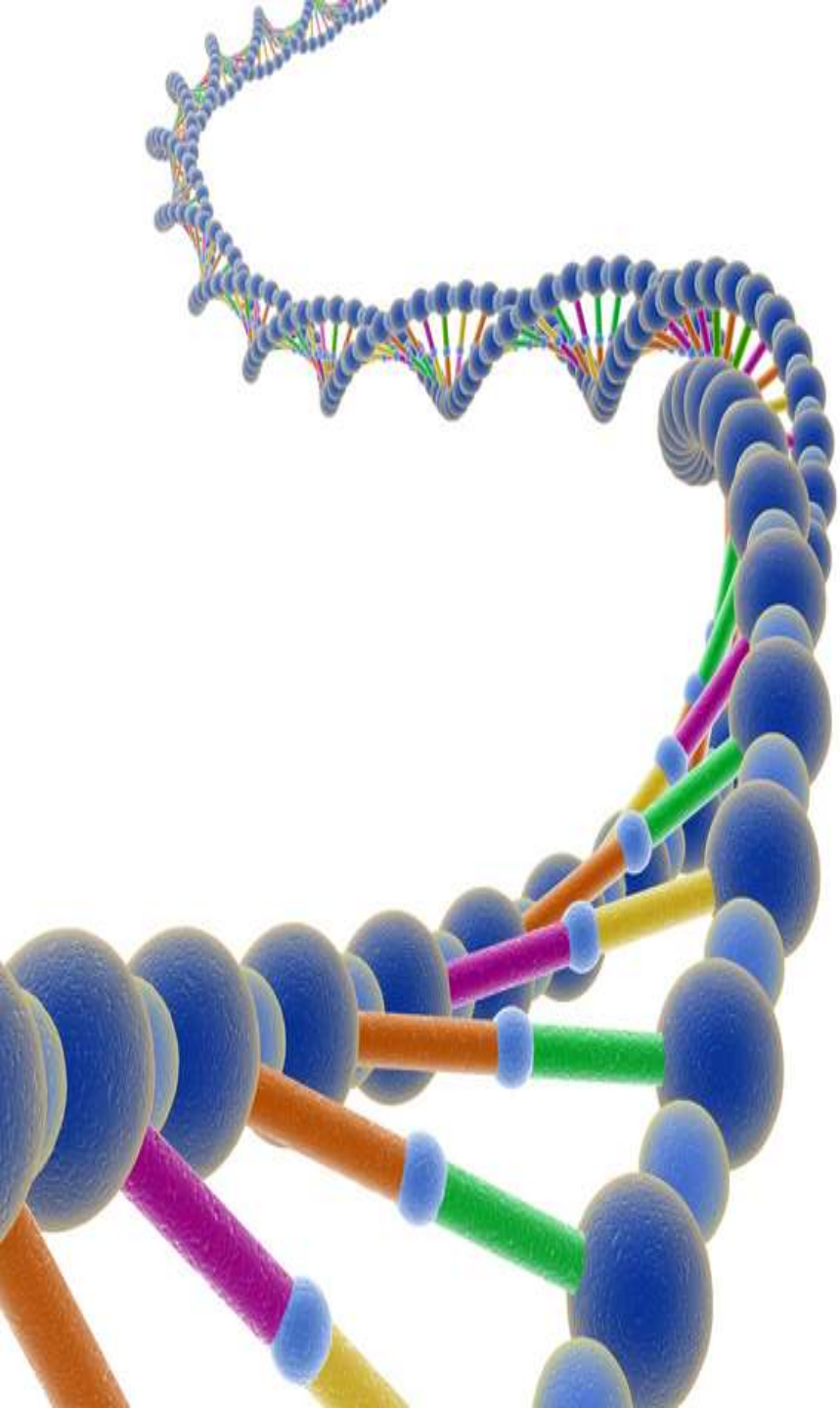
1. Nanji AA et.al. Lancet 1985; 1:681-83
2. Rotily M et.al. Eur J Clin Nut 1990;44:595-603
3. Park EJ et.al. CELL 2010;140:197-208

2) Obesity and associated hyperglycaemia increase incidence of all stages of ALD in heavy drinkers(4&5)

4. Raynard B et.al. Hepatology 2002;35:635-38
5. Naveau S et.al. Hepatology 1997;25(1):108-11

3) Steatohepatitis *and/or* diabetes are independent risk factors for cirrhosis and HCC (6-8)

6. Stickel F GUT 2010;59:1303-6
7. El Serag et.al. Gastroenterology 2004;126:460-8
8. Jee SH et.al. JAMA 2005;293:194-202



GENETICS:

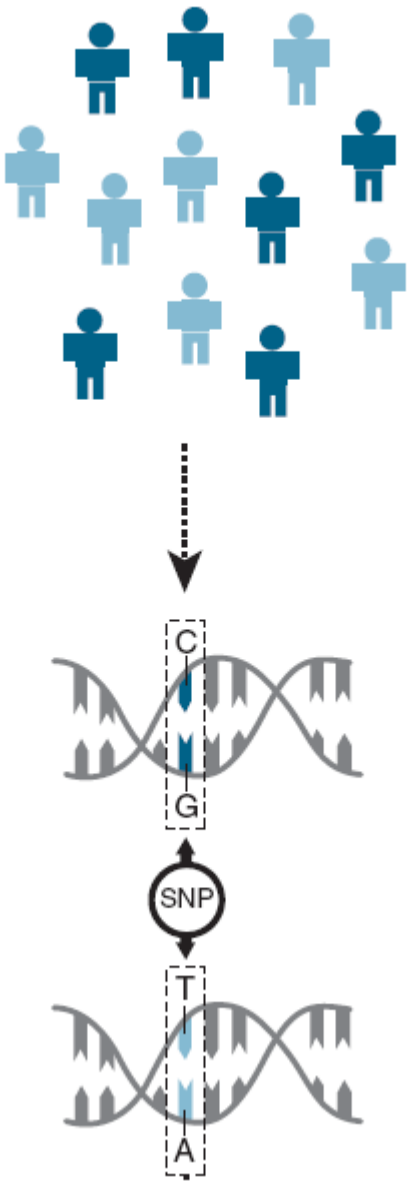
an important modulator of individual risk

- Twin studies show ALD concordance is 3X as likely in monozygotic than dizygotic twin pairings

Hrubec Z et.al. Alcohol Clin Exp Res 2002;26(supp):66S-69S

- Women more susceptible than men
- PNPLA3 rs738409(G) the first genetically confirmed risk factor for ALD

Stickel F et.al. GUT 2012;61:150-9



Genome wide association studies

I148M adiponutrin/patatin-like phospholipase domain-containing 3 gene (PNPLA3)

1. **NAS**: Romeo S*, et al.*. *Nat Genet* 2008; **40**:1461-5.

2. **ALD**: Stickel F*, et al. Hepatology* 2011; 53:86-95.
   Tian C, et.al. *Nat Genetics* 2010; **42**:21-23.
   Trepo E, *et al. J Hepatology* 2011; **55**:906-912

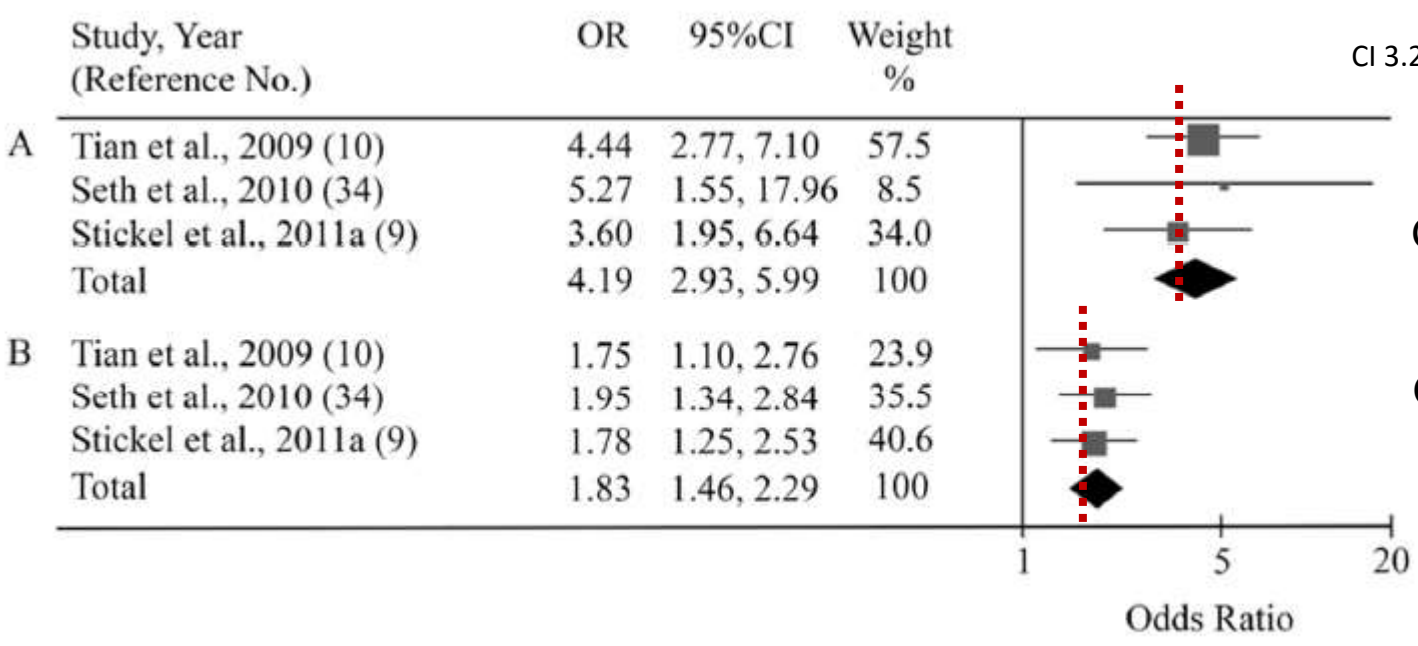
3. **NAFLD&HCC**: Sookoian S et.al. *Hepatology* 2011; **53**:1883-94.
   Trepo E*, et al.*. *Hepatology* 2013; Oct 1.

G allele confers a *higher risk of steatosis and/or fibrogenesis* in liver diseases, including:

- ALD
- Chronic hepatitis B and C infection, and
- Hereditary hemochromatosis.

The C>G SNP seems to be a risk factor in the development of advanced liver disease and hepatocellular carcinoma (HCC)

I148M (G>C Allele) association with Alcoholic Cirrhosis (ALC)



(OR 4.30, 95% CI 3.25–5.69; *P* < 0.00001

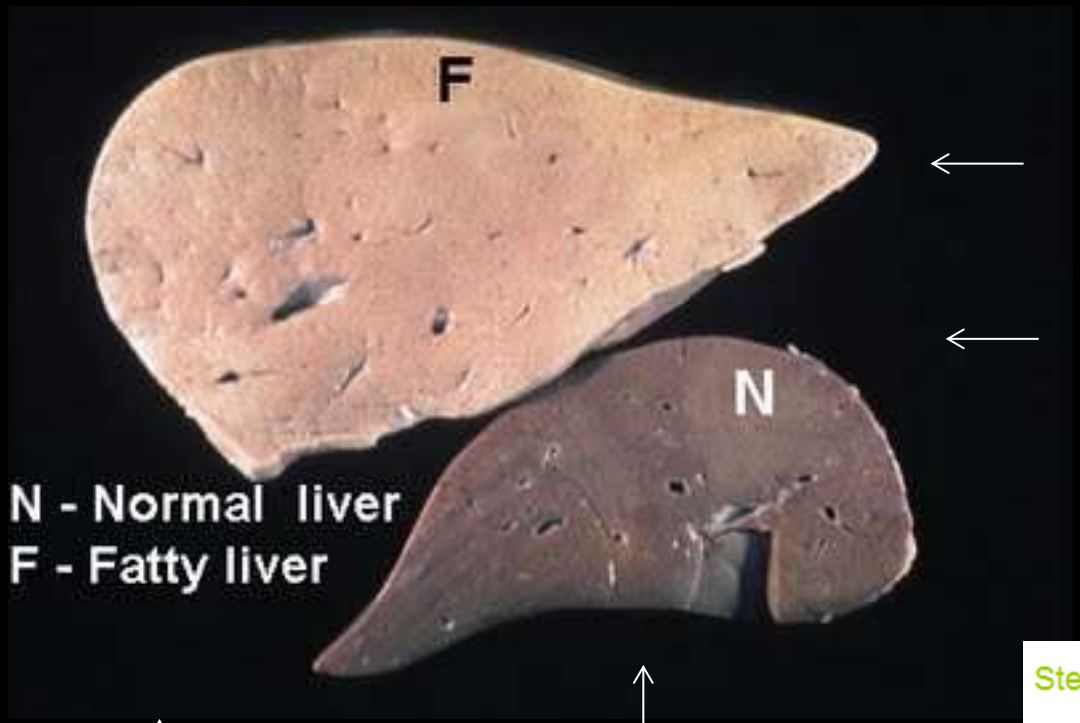
GG vs CC

GC vs CC

OR1.91, 95% CI 1.67–2.17; *P* < 0.00001,

Meta-analysis of the association of the rs738409 PNPLA3 polymorphism with ALC. *Patients with ALC as cases compared with alcoholics without liver disease.*

Chamorro A.J et.al. Aliment Pharmacol Ther 2014; Sept 40(6): 571-81

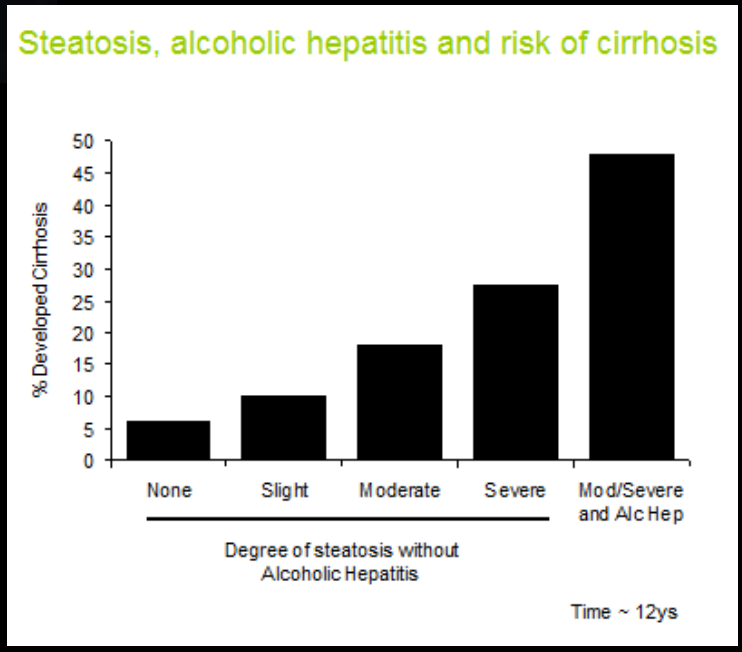


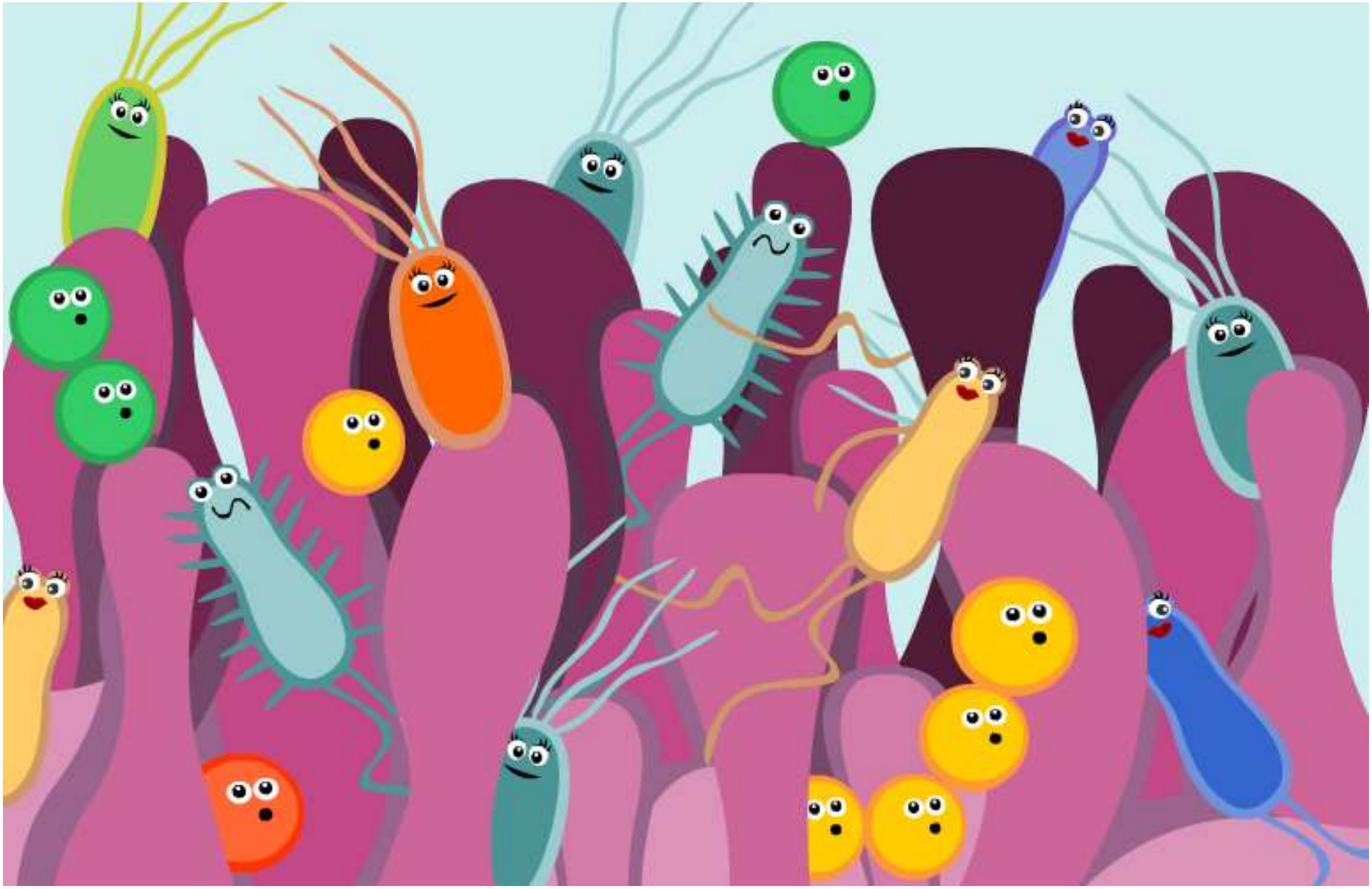
I148M is a major determinant of liver fat content and disease risk in ALD

I148M may independently determine fibrogenesis c.f its effects on liver fat

PNPLA3 increases risk of HCC

I148M modifies progression to steatohepatitis in alcoholic liver disease





Nan Qin Nature 2014 Volume: 513, Pages:59–64

Microbiome and Dysbiosis

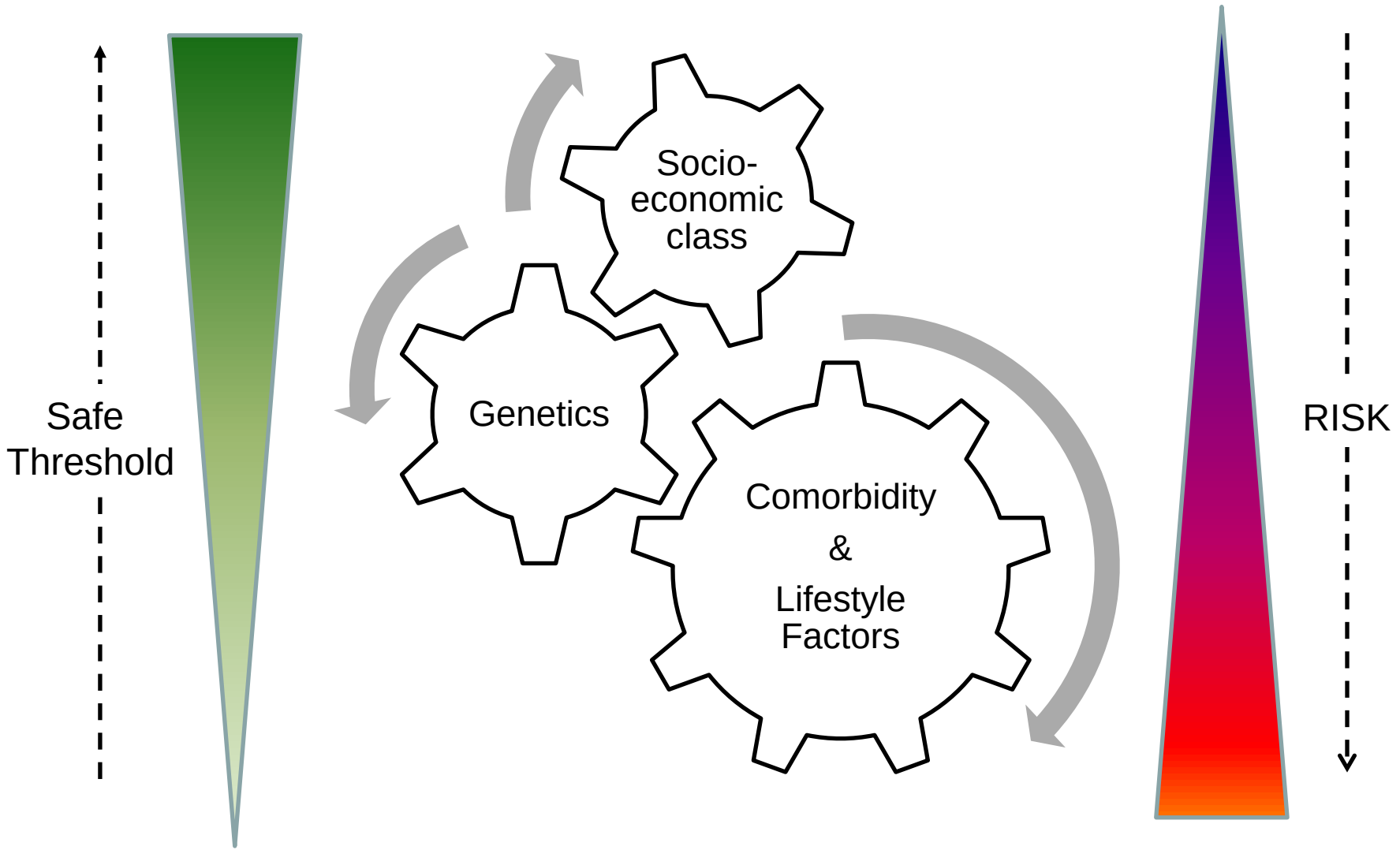
- CTP B8-C10 liver disease associated with increased gut permeability and translocation
- Microbiome dysbiosis increased in more advanced disease
- ArLD has a unique bile acid metabolome
- At similar MELD scores infected vs non-infected cirrhotics have very different flora
- Dysbiosis associated with increased IL-6, IL-1b & Secretory IgA

Inflammation

- IL-17/ENA/IL-8 – Neutrophil infiltrate
- IL12 signalling
- IL-17 levels correlate with mortality
- Actions on the target receptor IL-22R signals through STAT-3 upregulated in Alcoholic Hepatitis

Persistent inflammation/immunosuppression catabolism syndrome = immune senescence

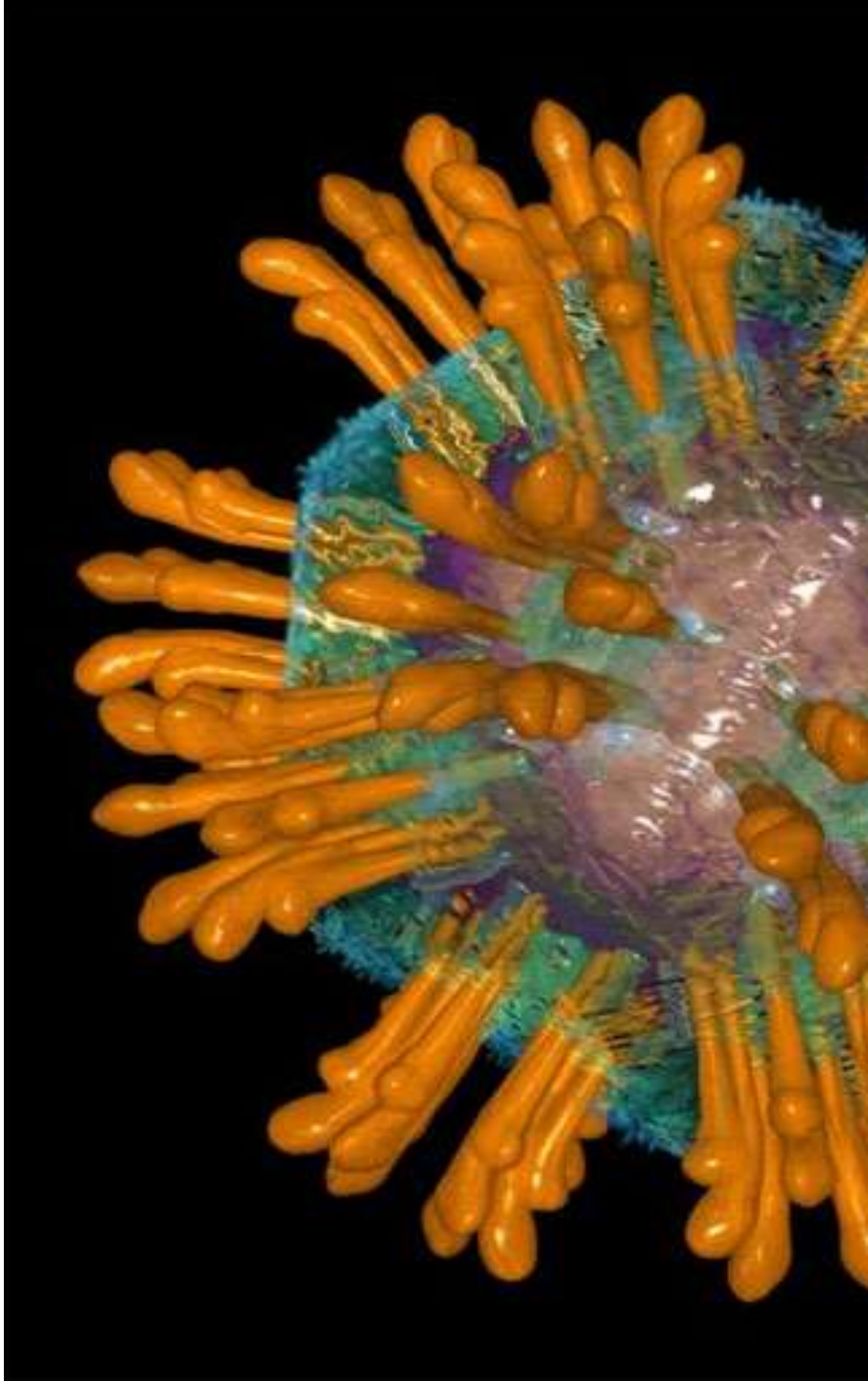
Alcohol Thresholds, Risk and Liver Disease



Viral liver disease

- Hepatitis B infection
- Hepatitis C infection

- Hepatitis D infection
- Hepatitis E



How NUCs have changed liver transplantation

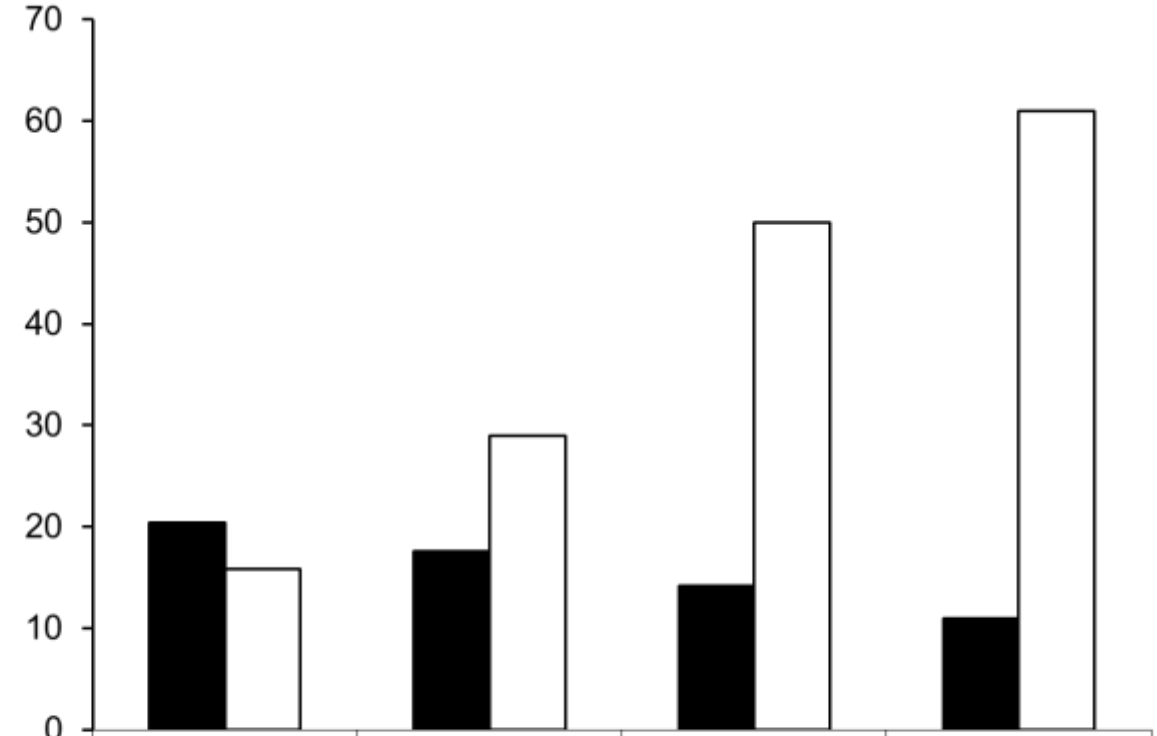
Chronic Hepatitis B

Cirrhosis

Liver failure

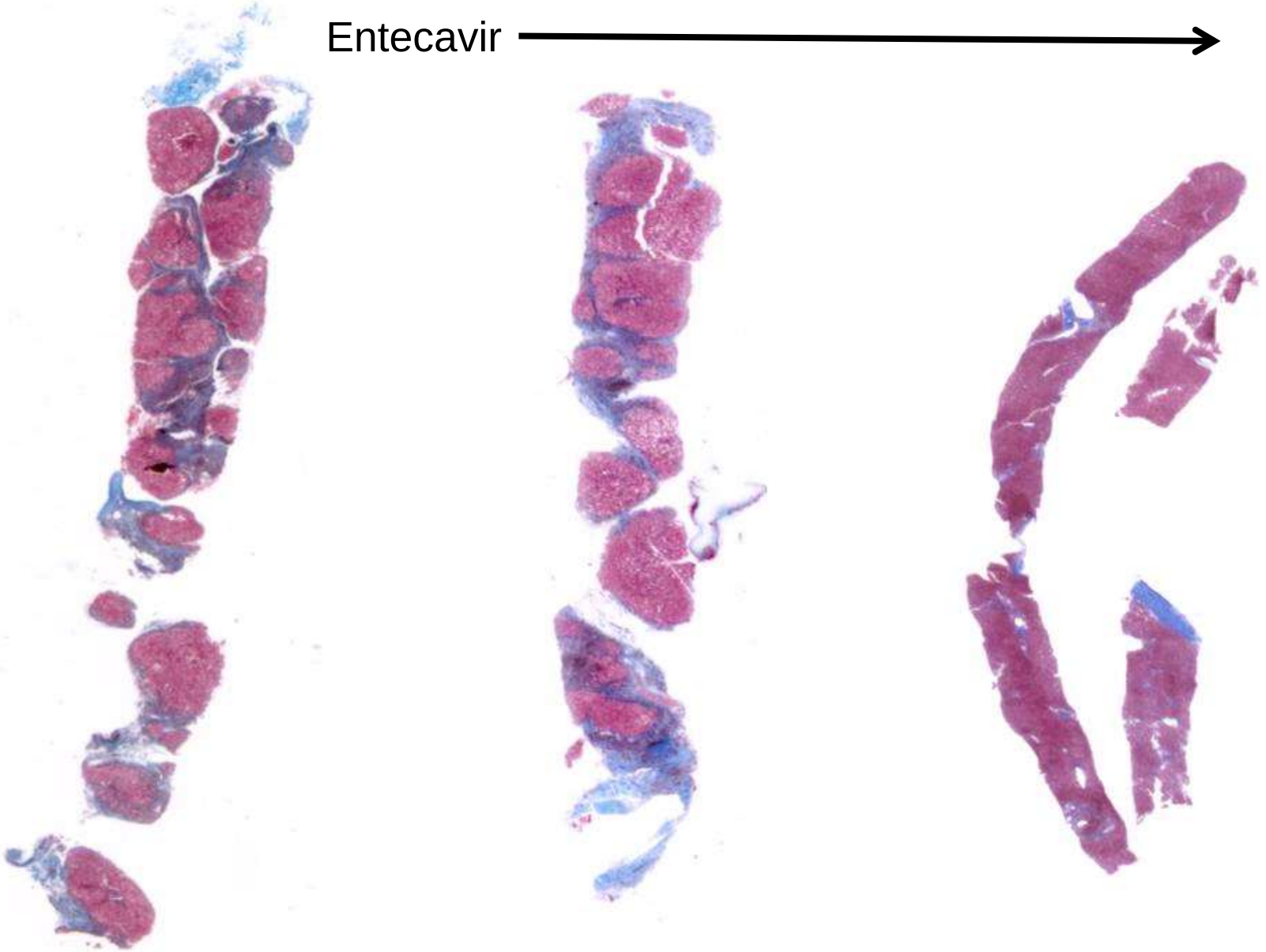
HCC

Transplantation /Death



	1991-5	96-2000	2001-5	2006-Jun10
■ Median MELD	20.4	17.6	14.2	11
□ % with HCC	15.8	29	50	61

Entecavir



Baseline
Ishak fibrosis=6

Week 48
Ishak fibrosis=6

Week 268 (5ys)
Ishak fibrosis=2

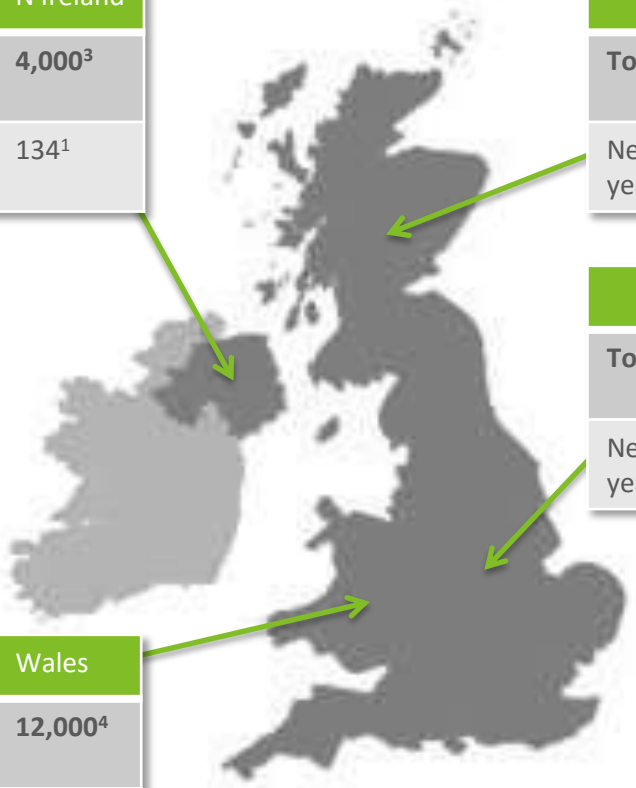
HCV impacts significant patient numbers in the UK[1]

	N Ireland
Total HCV Infection	**4,000[3]**
New diagnosis per year (2012)	134[1]

	Scotland
Total HCV Infection	**37,600[1]**
New diagnosis per year (2012)	1,991[1]

	England
Total HCV Infection	**160,000[1]**
New diagnosis per year (2012)	10,873[1,5]

	Wales
Total HCV Infection	**12,000[4]**
New diagnosis per year (2012)	480[1]



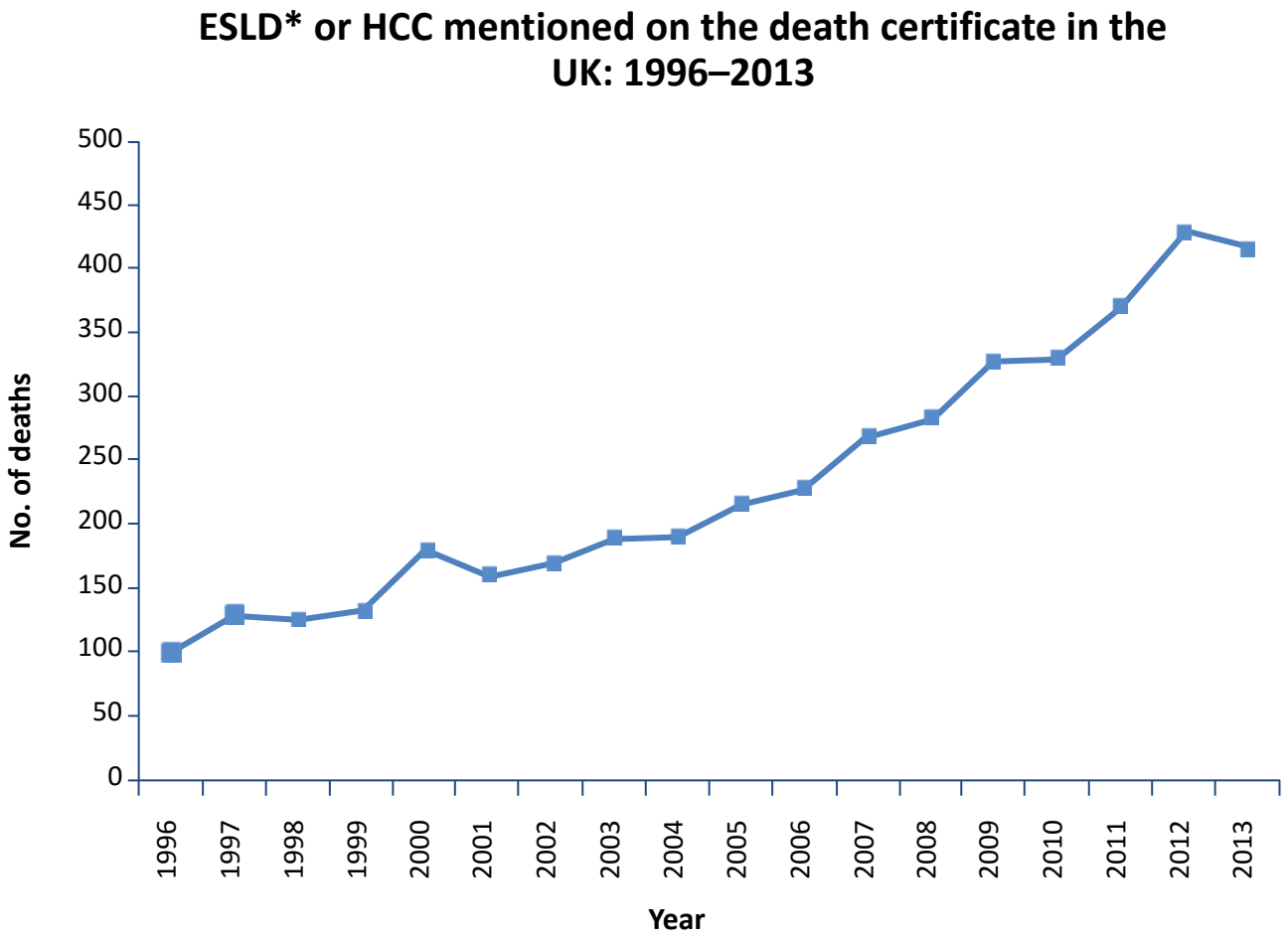
'Hot-spots' for HCV include[2]

- London
- Manchester
- Bristol
- Lancashire
- Blackburn
- Blackpool
- Liverpool
- Birmingham

90% G1 or G3

1. Health Protection Agency, Hepatitis C in the UK 2013. Accessed June 2014
2. HVA Action, Health and Wellbeing Boards & Hepatitis C: A review of the evidence from Joint Strategic Needs Assessments and Joint Health and Wellbeing Strategies, May 2014
3. Health and Safety Executive (HSE) website, Available at http://www.hse.gov.uk/biosafety/blood-borne-viruses/hepatitis-c.htm Accessed June 2014
4. Public Health Wales website, Available at: http://www.wales.nhs.uk/sitesplus/888/page/43746. Accessed June 2014
5. NHS Choices website. Available at: http://www.nhs.uk/conditions/hepatitis-c/pages/introduction.aspx Accessed on 8 May 2014

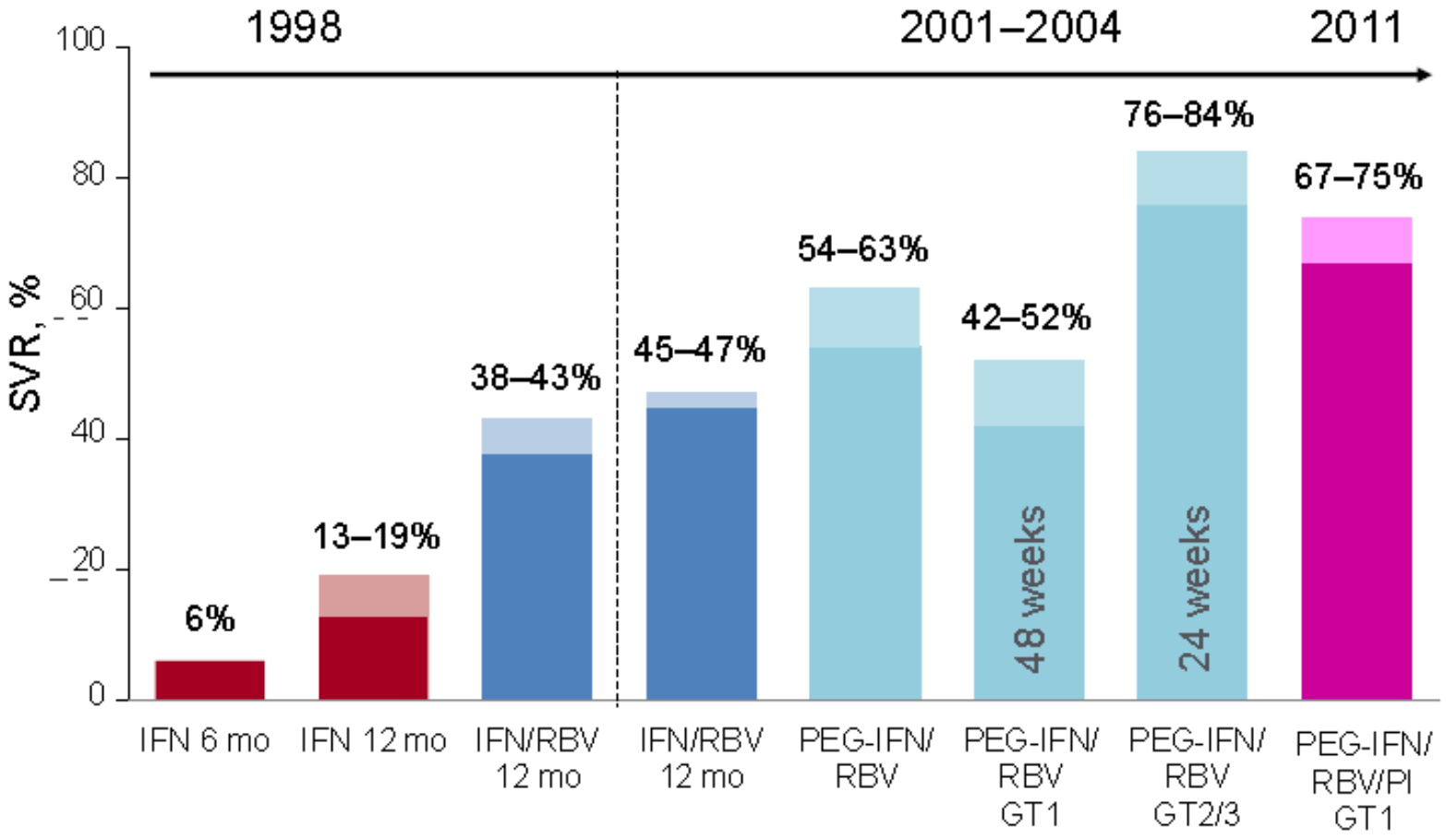
Deaths from HCV in the UK



ESLD = end-stage liver disease; HCC = hepatocellular carcinoma
* Defined by codes or text entries for ascites, bleeding oesophageal varices, hepatorenal syndrome, hepatic encephalopathy or hepatic failure

Public Health England. Hepatitis C in the UK 2015 report (accessed August 2015).

Treatment timeline of chronic hepatitis C



Adapted from Cornberg et al Hepatology 2013

IFN trials
USA trial: McHutchison NEJM 1998
International trial: Poynard Lancet 1998

PEG-IFN trials
PEG-IFN2b: Manns Lancet 2001
PEG-IFN2a: Fried NEJM 2002; Hadziannis Ann Int Med 2004

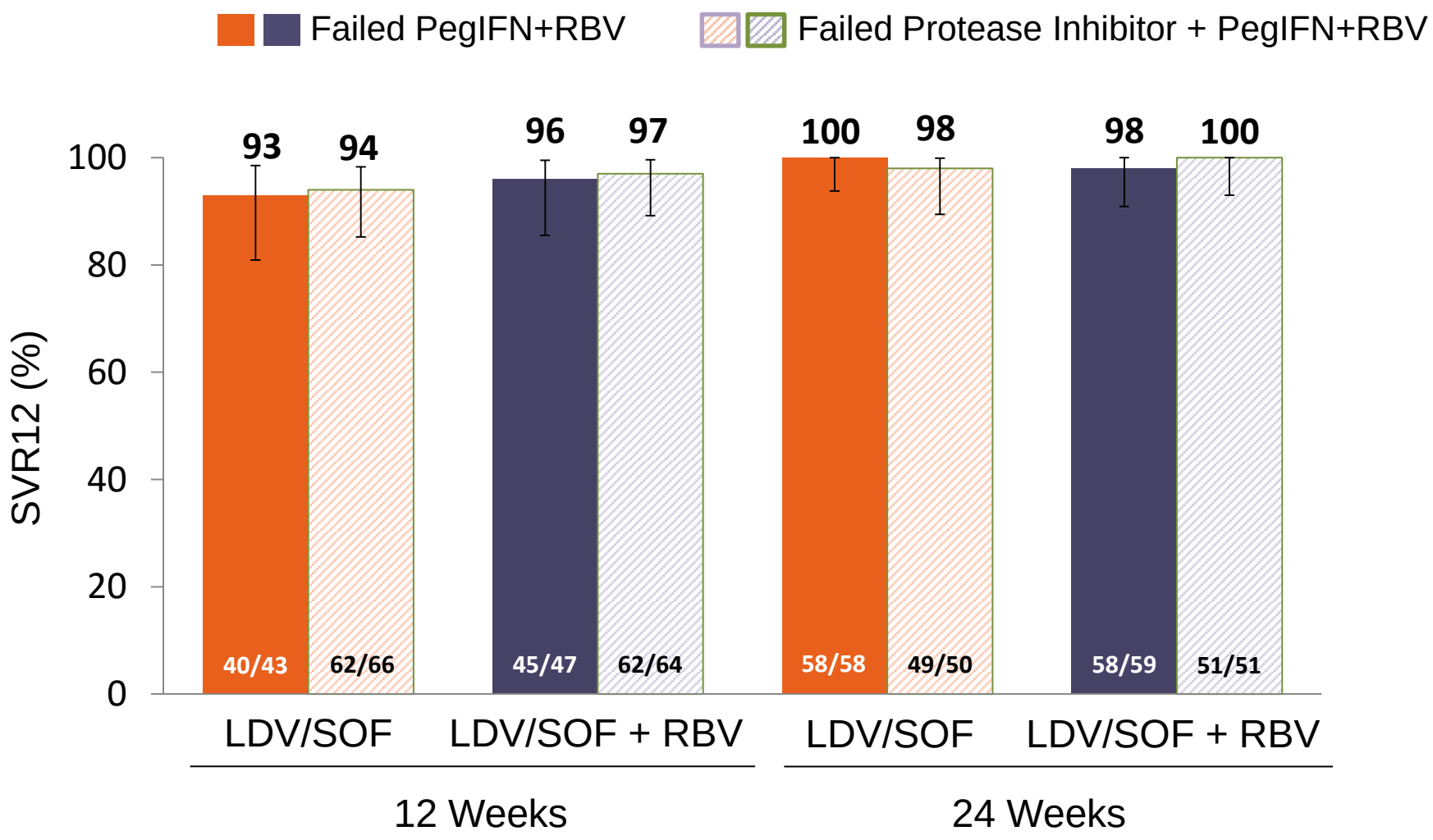
PI trials
Boceprevir: Poordad NEJM 2011 (non-black cohort)
Telaprevir: Jacobsen NEJM 2011

“The past is a foreign country: *they do things differently there...“*

L.P. Hartley

The Go Between: 1953

ION-2 Treatment Experienced

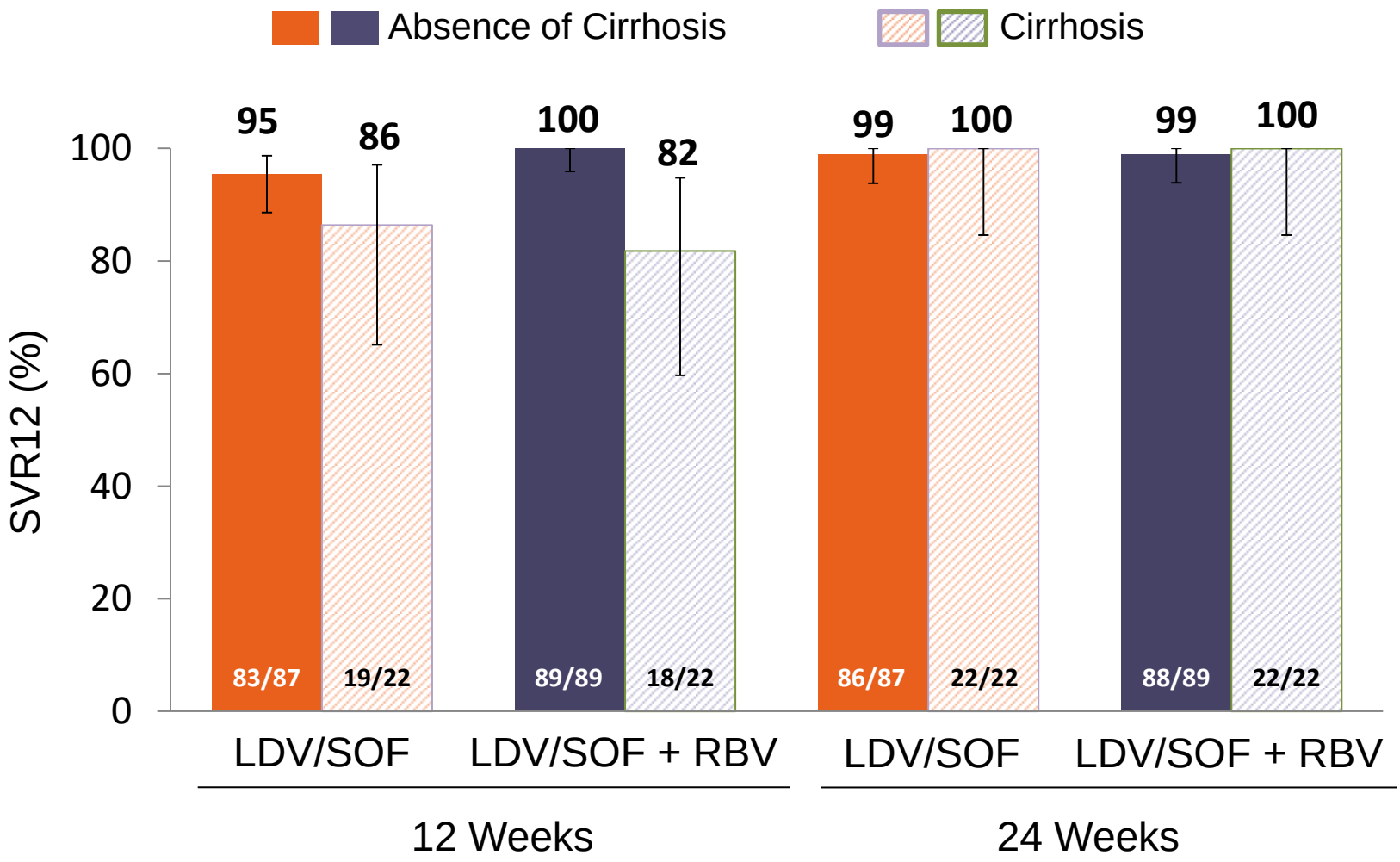


Error bars represent 95% confidence intervals

Afdhal N, EASL, 2014, O109

Afdhal N, et al. *N Engl J Med* 2014; 2014 Apr 12 [Epub ahead of print]

ION-2 Treatment Experienced

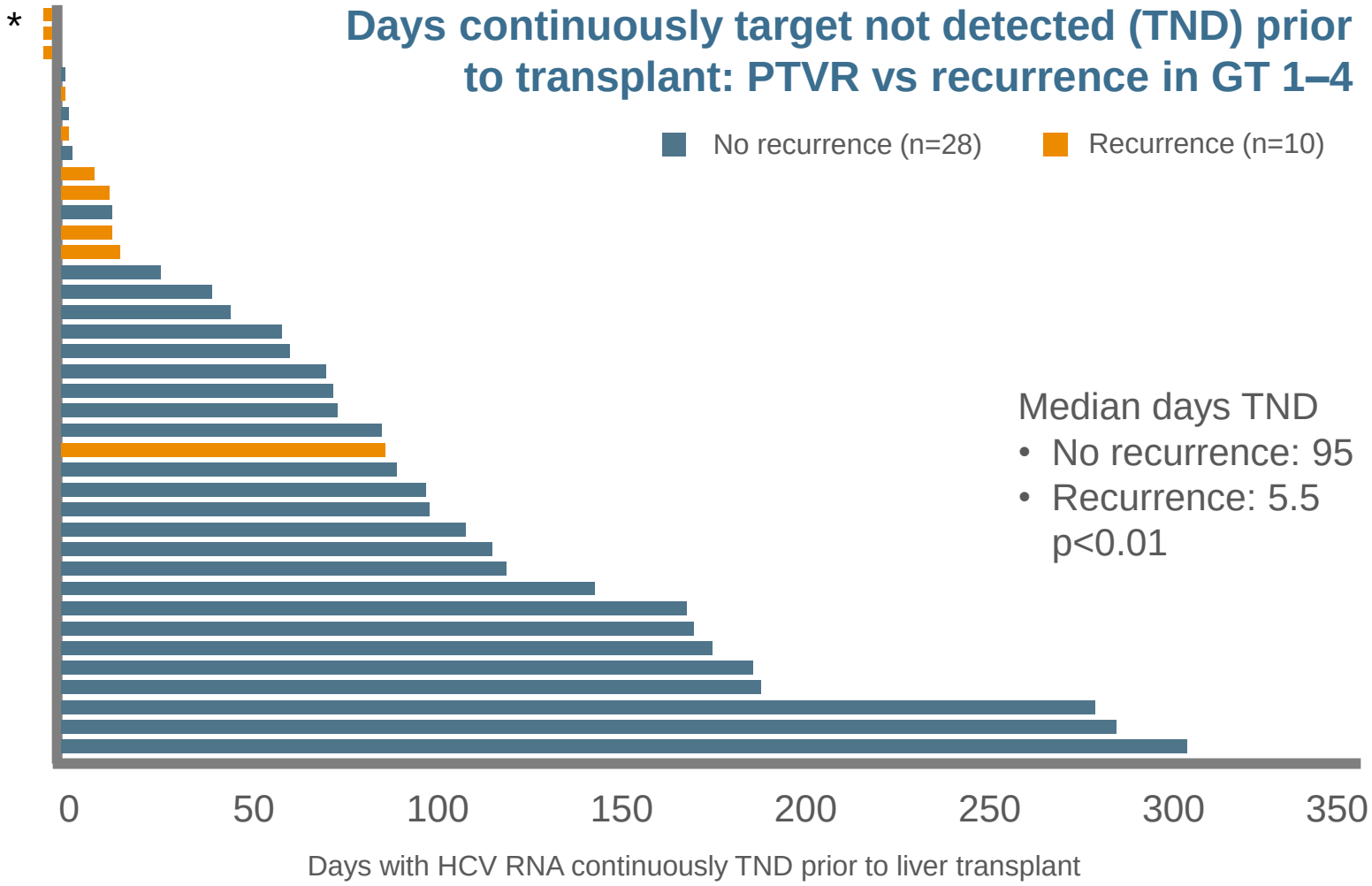


Error bars represent 95% confidence intervals

Afdhal N, EASL, 2014, O109

Afdhal N, et al. *N Engl J Med* 2014; 2014 Apr 12 [Epub ahead of print]

Study 2025: no recurrence vs recurrence in GT 1–4

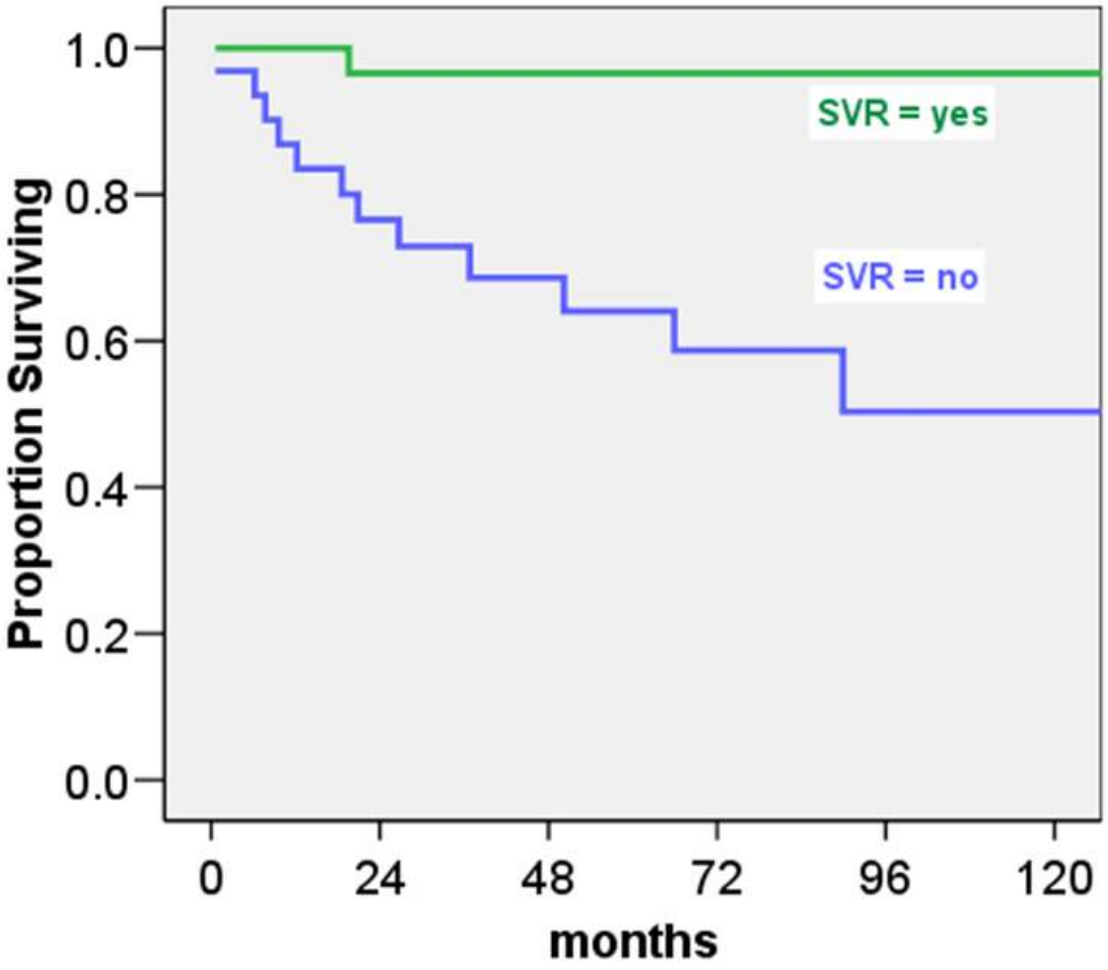


*3 patients with recurrent HCV had 0 consecutive days TND before transplant

Curry MP et al. AASLD 2013, oral 213

HCV Treatment Post-LT

Patient survival vs treatment outcome



(Birmingham unpublishe

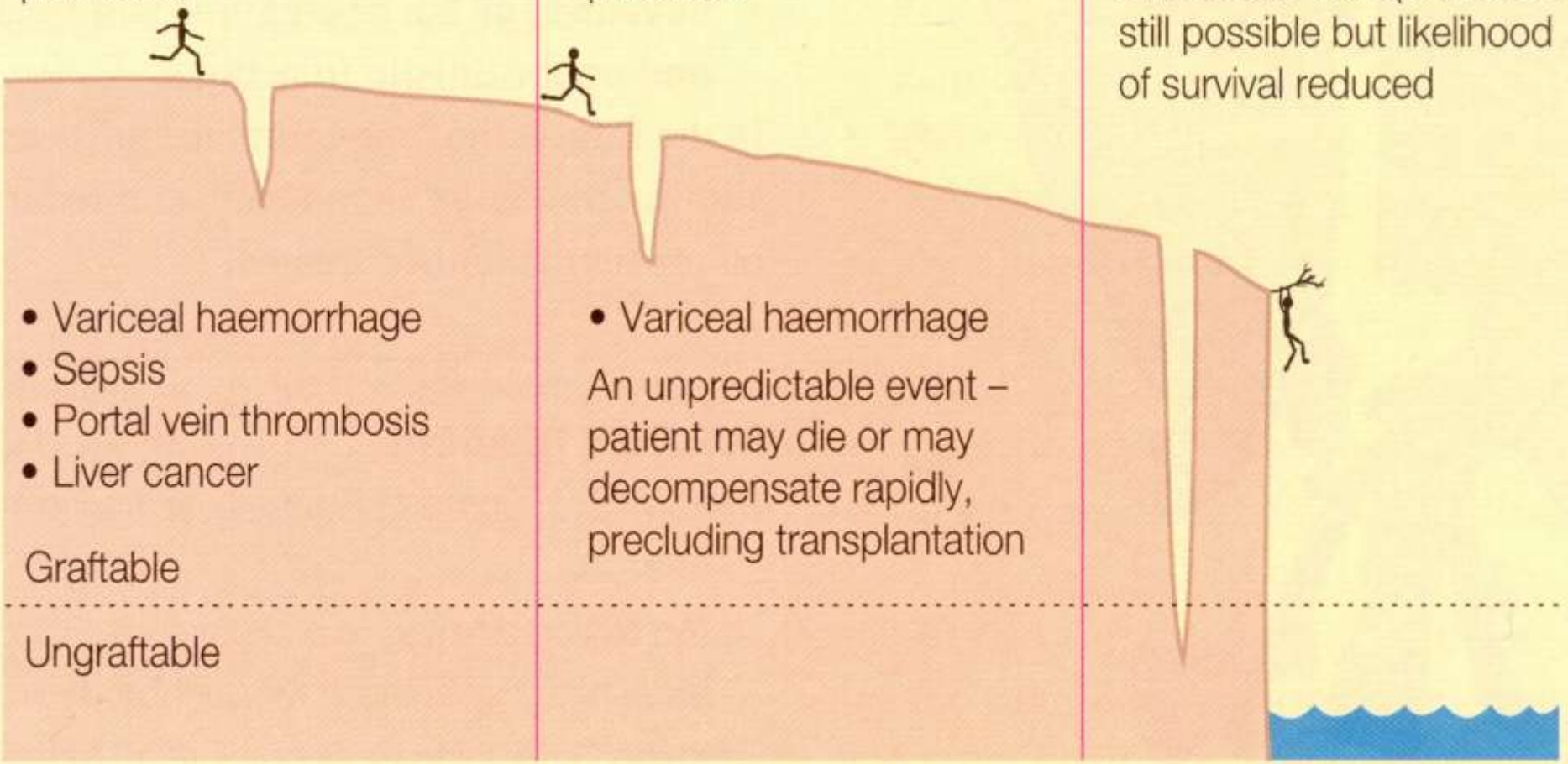
pharma	Protease Inhibitor	NS5A inhibitor	Polymerase Inhibitor	ribavirin	duration (weeks)	cure rate	comments
MSD	MK 5172	MK 8742		not needed	12	>90%	including prior IFN non-responders
Gilead ION-1		Ledipasvir	Sofosbuvir	not needed	12	>90%	treatment-naïve
Gilead ION-2		Ledipasvir	Sofosbuvir	not needed	12 - 24	80-100%	including prior PI non-responders
AbbVie	ABT450 /ritonavir	Ombitasvir	Dasabuvir	always included	12	>90%	including prior IFN non-responders
Gilead Janssen	Simeprevir		Sofosbuvir	not needed	12	>90%	including prior IFN non-responders

Child–Pugh score and prognosis

Child–Pugh A
Prolonged survival expected in most patients – referral premature

Child–Pugh B
Suitable time for patient referral – good results predicted

Child–Pugh C
Transplantation becoming a higher-risk procedure
Successful transplantation still possible but likelihood of survival reduced



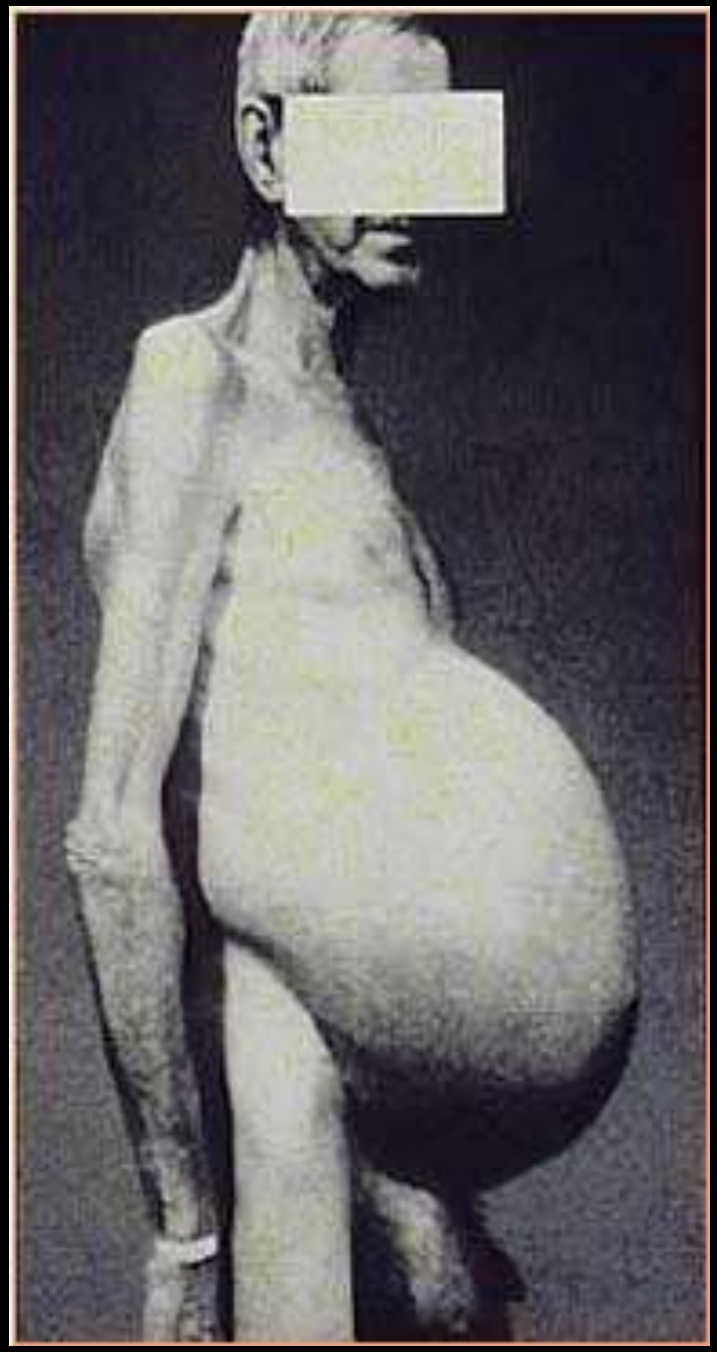
- Variceal haemorrhage
- Sepsis
- Portal vein thrombosis
- Liver cancer

Graftable

Ungraftable

- Variceal haemorrhage

An unpredictable event – patient may die or may decompensate rapidly, precluding transplantation



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Sequana Medical signs collaboration agreement with Fresenius Medical Care for the marketing and distribution of the alfapump® system

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Sequana Medical presents exciting clinical updates on the alfapump® System at this year's International Liver Congress in Vienna.

››› find out more

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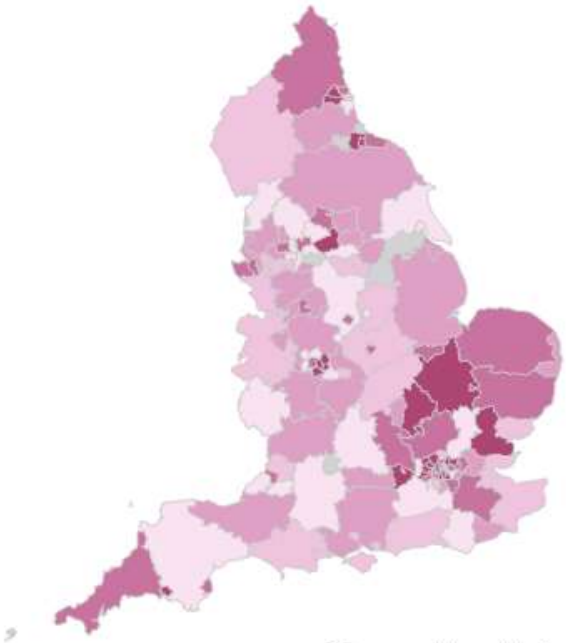
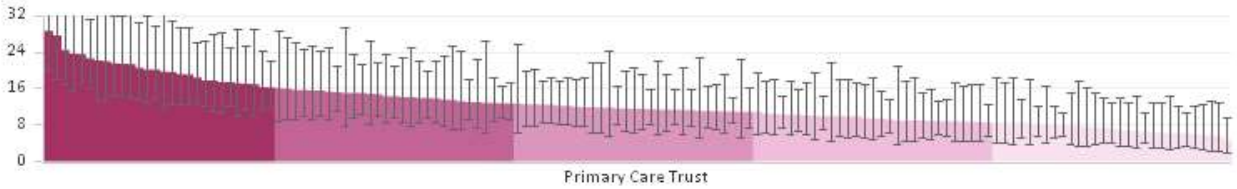
Liver Transplant by residence in PCT

Rate of liver transplantation per 100,000 population, by PCT,: 2006/7 - 2010/11





Metadata | Help

- Not Applicable
- Lowest value
- Highest value
- Data unavailable or missing

Area name	Value
East Riding Of Yorkshire	4.5
Greenwich Teaching	5.5
Salford	5.6
Hull Teaching	5.7
Nottingham City	5.9
Wiltshire	6
Solihull	6.1
North Lancashire Teaching	6.1
West Essex	6.2
Sunderland Teaching	6.2
Oxfordshire	6.5
Barnsley	6.6
East Sussex Downs and Weald	6.7
Walsall Teaching	6.8
East Lancashire Teaching	7.2
Dudley	7.3

www.sepho.org.uk/extras/maps/NHSatlasLiver/atlas.html