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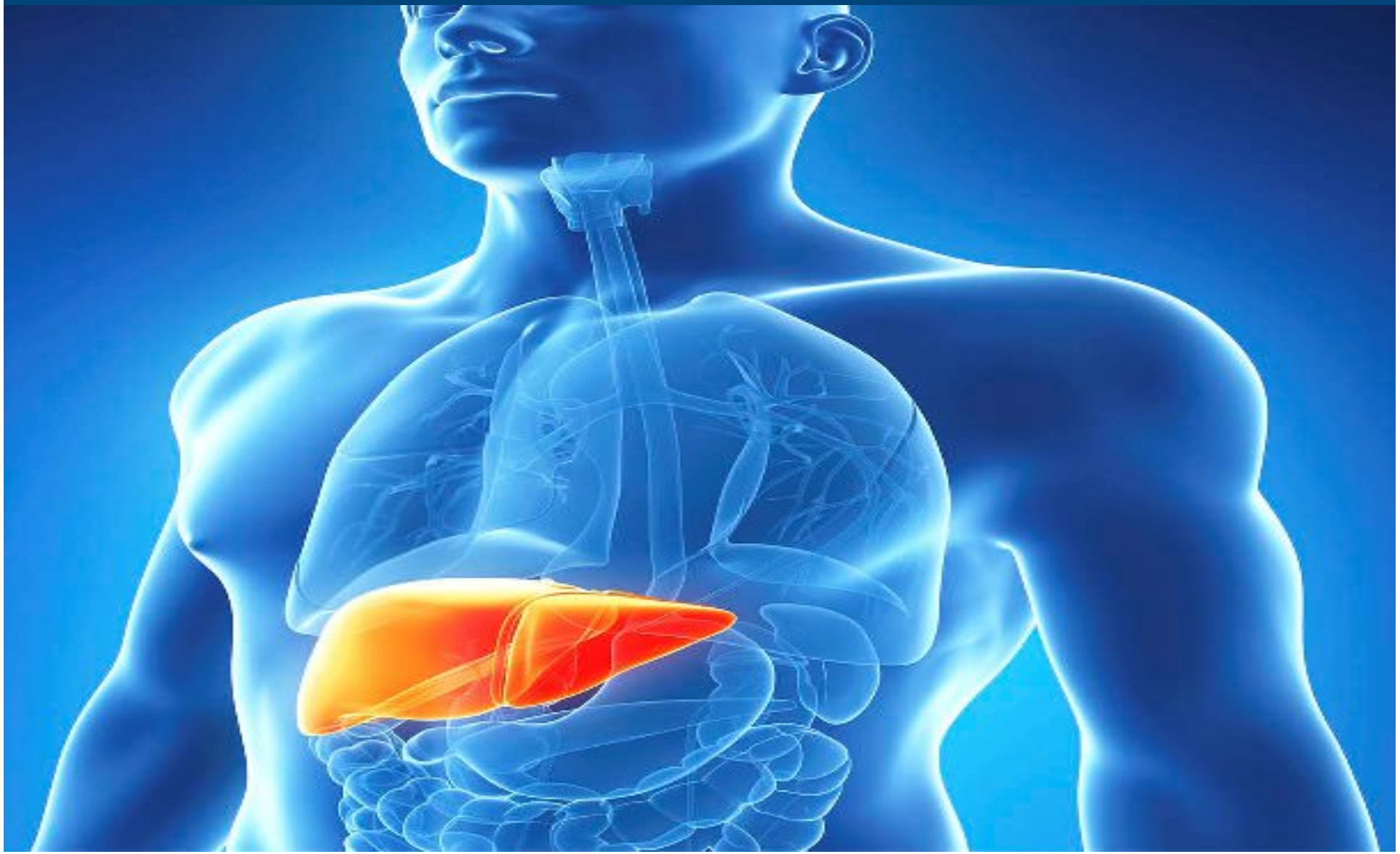
Stratified Medicine for Hepatitis C Infection



Hepatitis C Infection – a Clinical Challenge Across the UK

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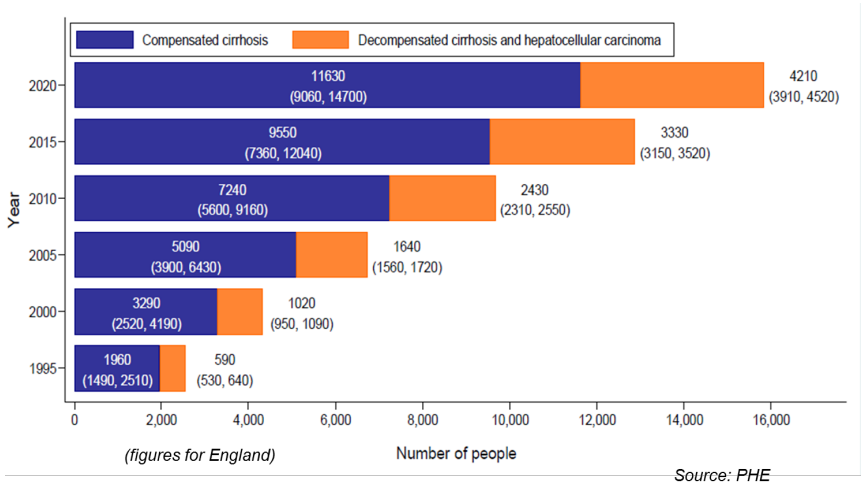
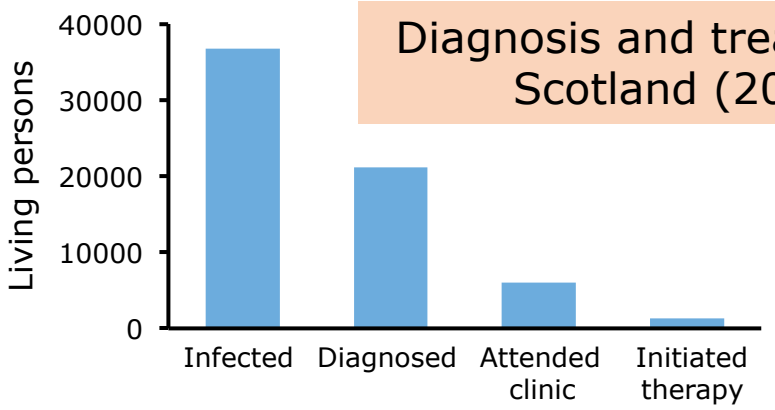
Stratified Medicine for HepC

Infections in UK
n=214,000

Increasing incidence of cirrhosis and severe liver disease



Source: PHE



Diagnosis and treatment in Scotland (2014)

STOP-HCV and HCV Research UK – Addressing the Challenges of Hepatitis C

HCV Research UK

- Establish a national cohort of infected patients to promote research
- Create an infrastructure to collect and release clinical data and samples for studies on in vivo infection
- £2M funding from the Medical Research Foundation (2011)

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- Derive stratification models to enhance clinical decision making
- Understand disease mechanisms that define patient strata for developing rational therapeutic approaches
- £5.2M funding from the Medical Research Council (2013)

The HCV Research UK Clinical Network

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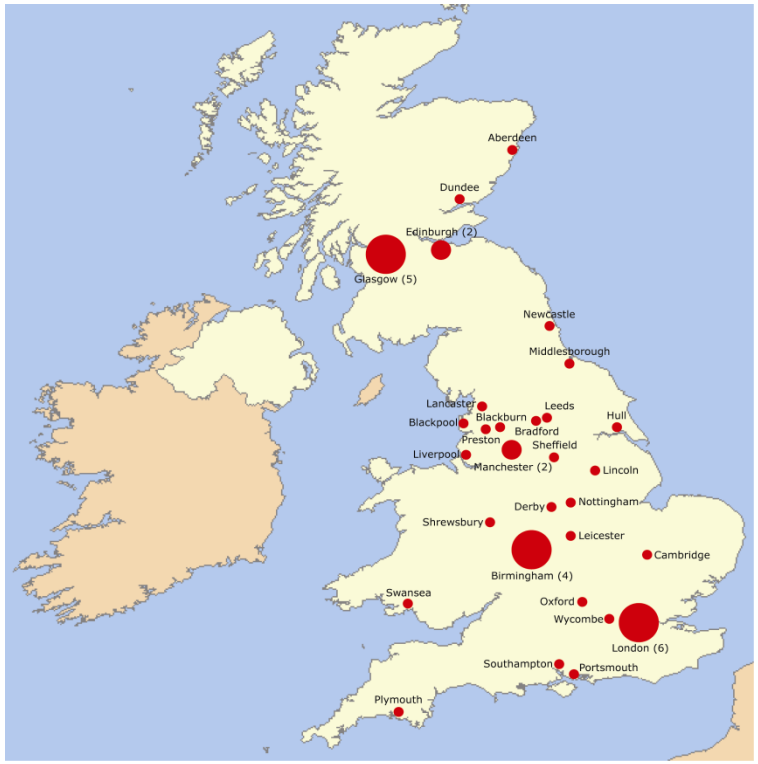
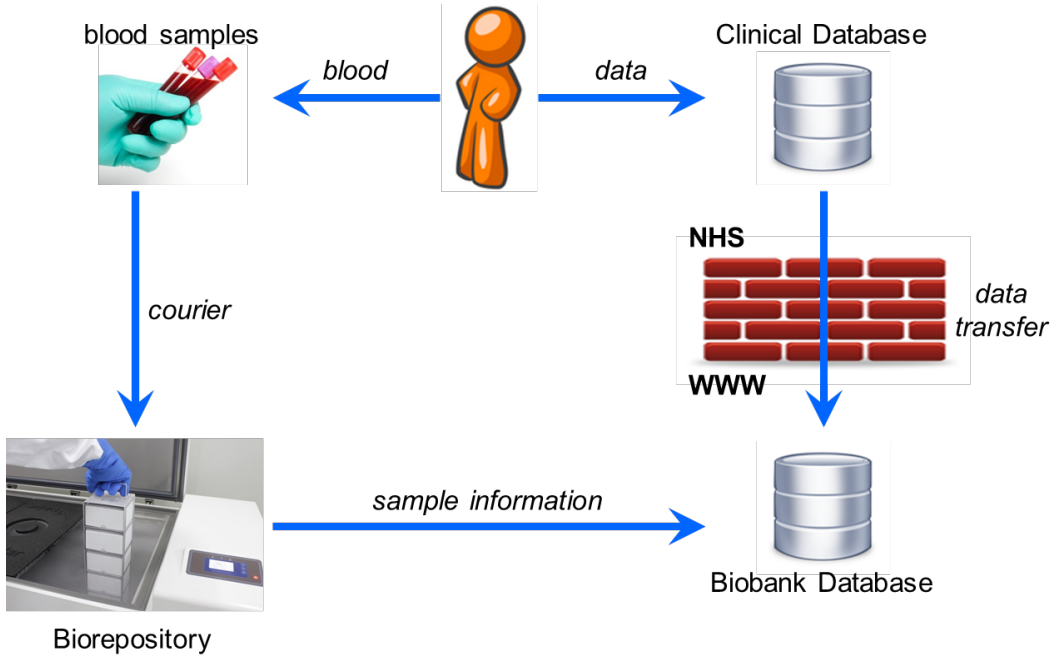
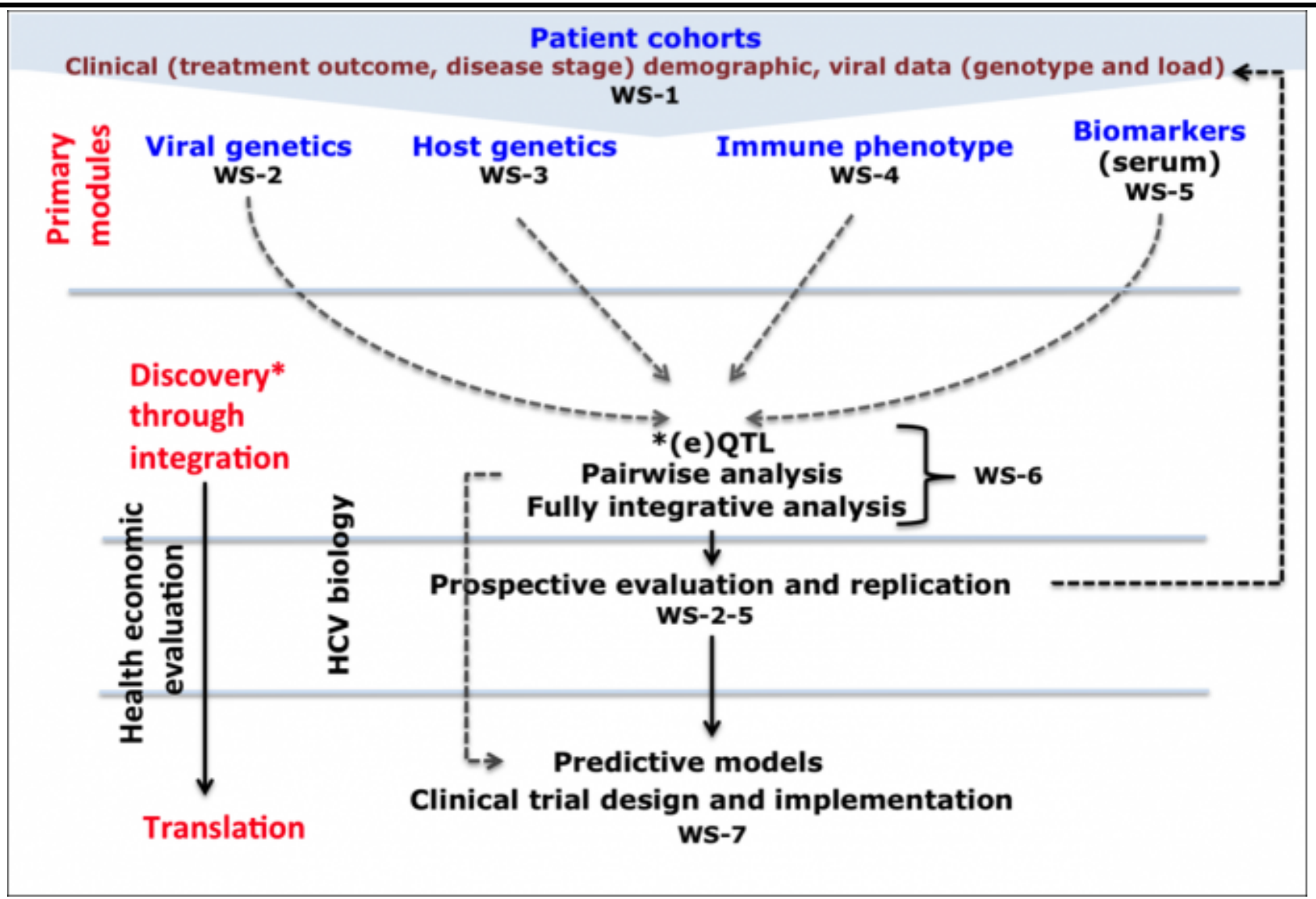
57 clinical centres



Centralised system for data and sample collection



Integration of the Scientific Outputs of STOP-HCV



Direct-Acting Antivirals (DAAs) – The New Era of Hepatitis C Therapy

NS3(pro)	NS5A	NS5B
Protease Inhibitors	NS5A Inhibitors	Polymerase Inhibitors
Simeprevir	Ledipasvir	Sofosbuvir
Paritaprevir	Daclatasvir	Dasabuvir
grazoprevir	Ombitasvir	
	Velpatasvir	
	Elbasvir	

Direct-Acting Antivirals (DAAs) – The New Era of Hepatitis C Therapy

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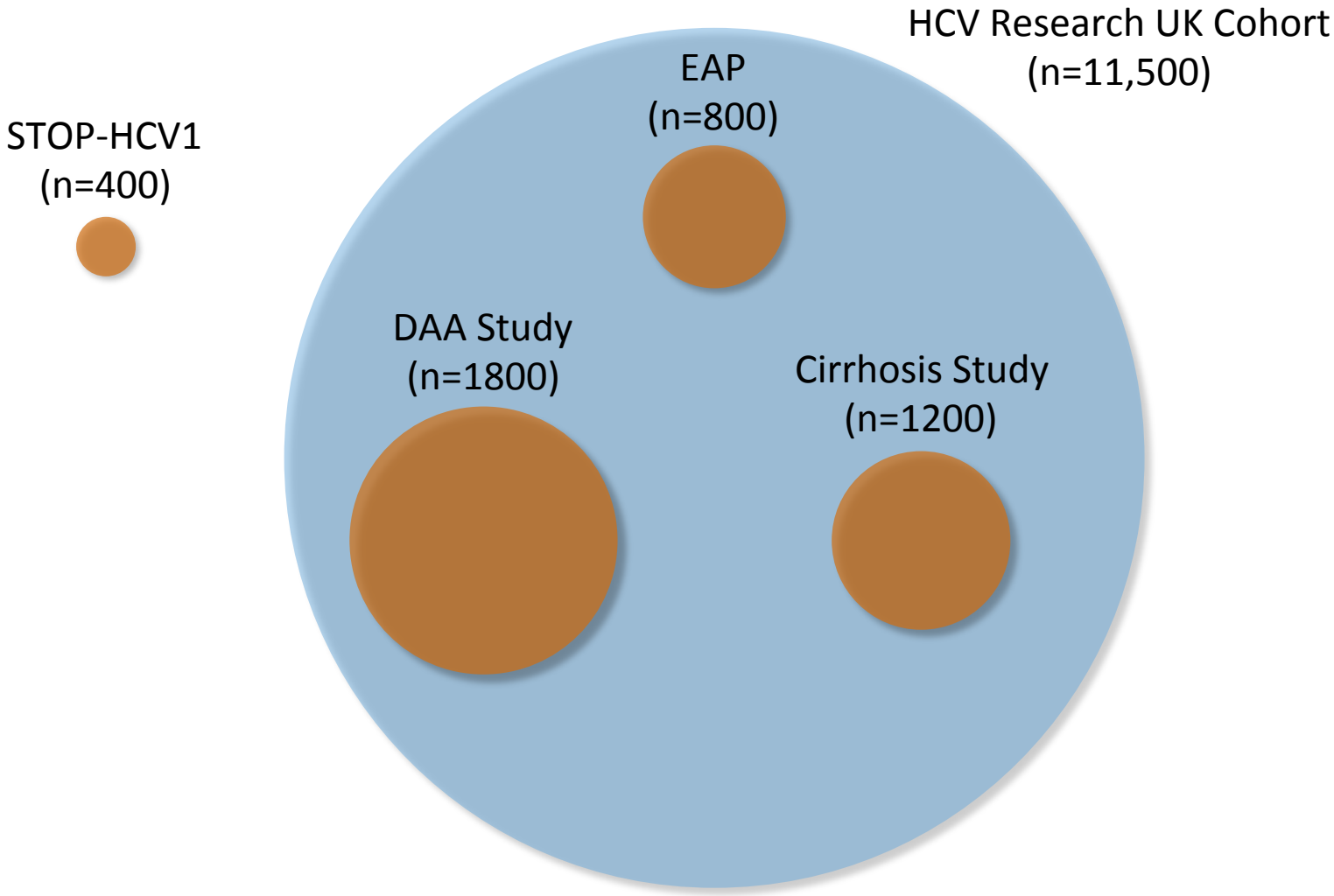
NS3(pro)	NS5A	NS5B
Protease Inhibitors	NS5A Inhibitors	Polymerase Inhibitors

How Effective are the DAAs in Real World Cohorts?

- grazoprevir
- Ombitasvir
- Velpatasvir
- Elbasvir

Real World Cohorts to Assess the Outcomes of DAA Therapy



Innovations in NGS - Multiplexing and Detection of Resistance Substitutions

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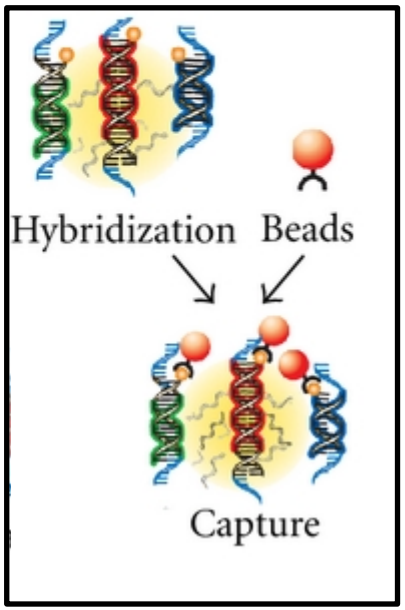
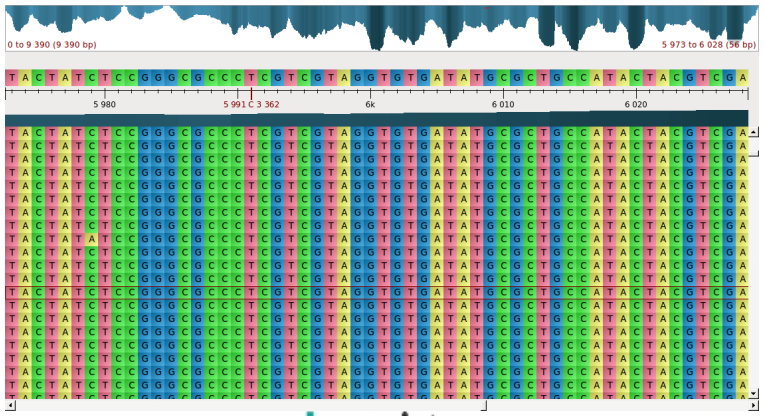
AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology

Comparison of Next-Generation Sequencing Technologies for Comprehensive Assessment of Full-Length Hepatitis C Viral Genomes

Emma Thomson,[a] Camilla L. C. Ip,[b] Anjna Badhan,[d] Mette T. Christiansen,[e] Walt Adamson,[a] M. Azim Ansari,[c] David Bibby,[d] Judith Breuer,[e] Anthony Brown,[c] Rory Bowden,[b] Josie Bryant,[e] David Bonsall,[c] Ana Da Silva Filipe,[a] Chris Hinds,[a] Emma Hudson,[c] Paul Klenerman,[c] Kieren Lythgow,[d] Jean L. Mbisa,[d] John McLauchlan,[a] Richard Myers,[d] Paolo Piazza,[b] Sunando Roy,[e] Amy Trebes,[b] Vattipally B. Sreenu,[a] Jeroen Witteveldt,[f] STOP-HCV Consortium, Eleanor Barnes,[c] Peter Simmonds[c,f]





Public Health England

HCV-GLUE for Rapid Genotyping and Detection of Resistance Substitutions

HCV-GLUE | Home | Sequence Database | Drug Resistance | Analysis

Submit your sequence files in FASTA nucleotide format for automated analysis of the sequence type and interpretation of the nucleotide content.

File	Size	Variation categories	Status	Actions
AA44_1-Ref.1a.x.x.LTD62XF224.AF511950.fasta	0.01 MB	Resistance-associated variants	✔	Show analysis | Remove

Add files | Remove all files

Analysis Results

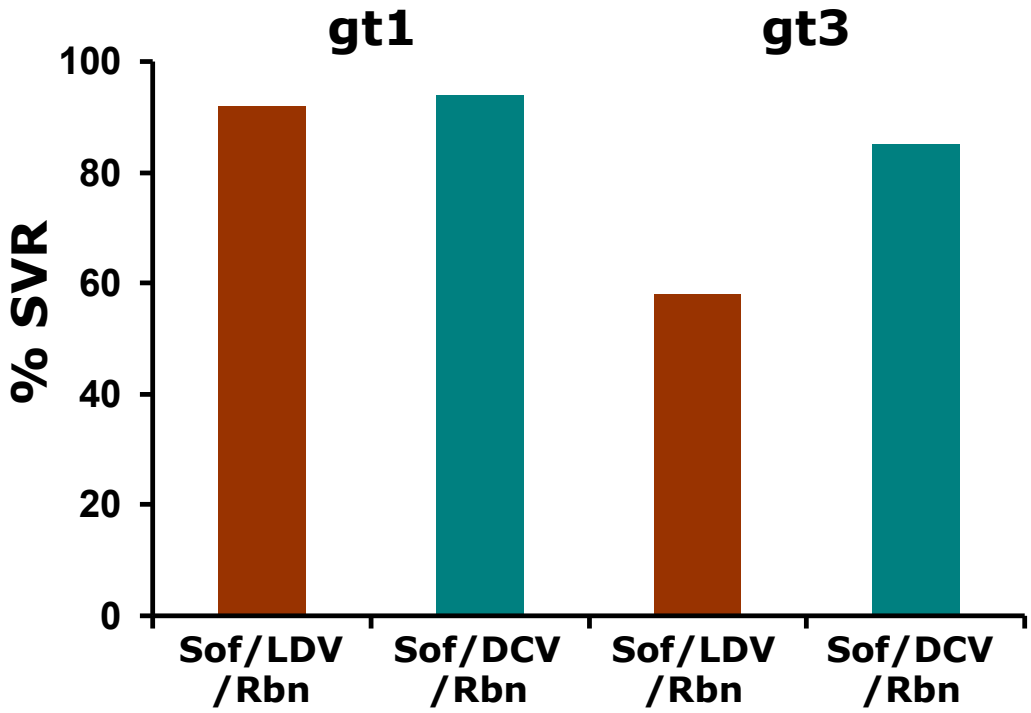
Typing summary | Variation summary | Genome detail

File	Query sequence	Variation category
AA44_1-Ref.1a.x.x.LTD62XF224.AF511950.fasta	AA44_1-Ref.1a.x.x.LTD62XF224.AF511950.sam 5208	Resistance-associated variants

Resistance-associated variants where a match was found in the query sequence: 4

Reference sequence	Genome feature	Resistance-associated variants		
H77_AF009606	NS3	NS3:175L		
H77_AF009606	NS5A	NS5A:28M	NS5A:30Q	NS5A:31I

The DAA Experience with the Expanded Access Programme



- HCV gt3 responds less well to therapy
- About 3% of patients misdiagnosed for viral genotype
- Genotype switching between pre- and post-therapy for some relapsers
- Rare subtypes respond less well to therapy

Does Cure of Infection Affect Liver Disease Prognosis?

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Research Article

EASL JOURNAL OF HEPATOLOGY

Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy☆

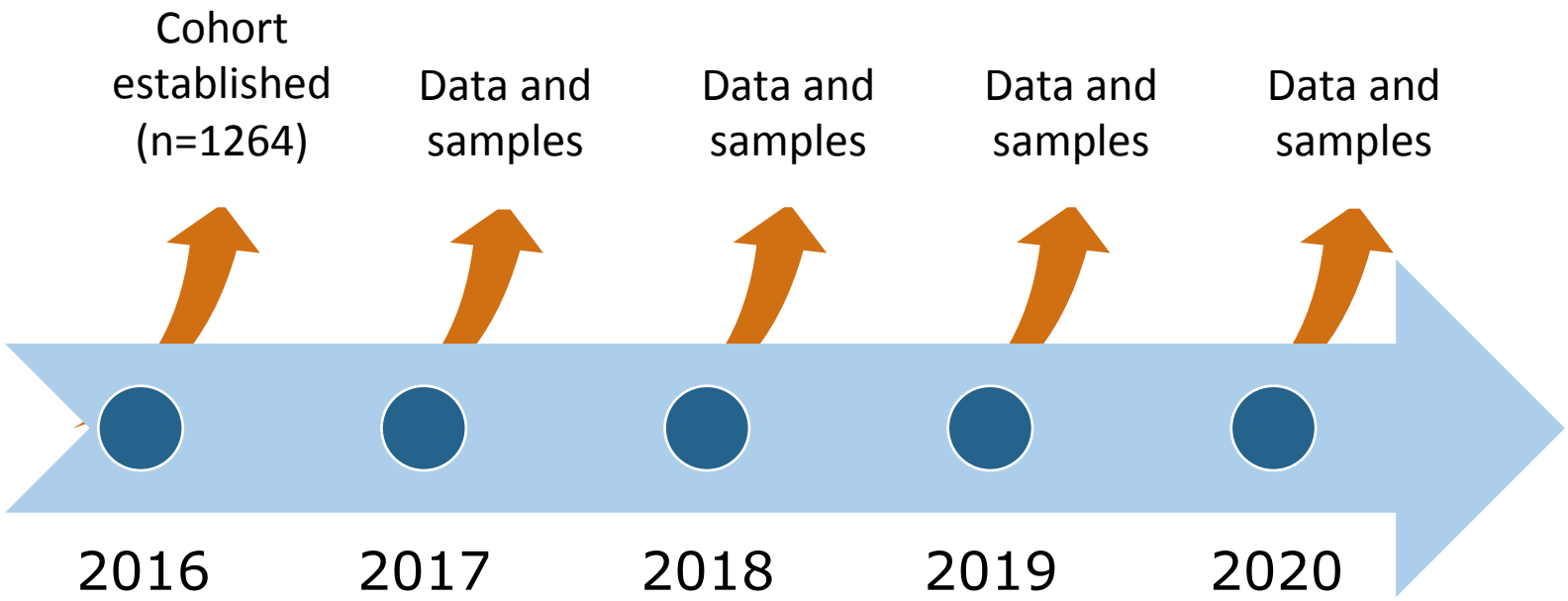
Letters to the Editor

EASL JOURNAL OF HEPATOLOGY

Unexpected high incidence of hepatocellular carcinoma in cirrhotic patients with sustained virologic response following interferon-free direct-acting antiviral treatment

Unexpected high incidence of hepatocellular carcinoma in patients with hepatitis C in the era of DAAs: Too alarming?

Long-term Outcomes – The Longitudinal Cirrhosis Study



- Extensive host genotyping
- Viral sequences for all patients
- Responses to therapy
- Identify and validate markers for HCC

What about the Future?

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STOP-HBV

With thanks to…

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University of Birmingham
University of Bristol
University of Dundee
University of Glasgow
The University of Nottingham
University of Southampton
Queen Mary University of London
University of Oxford
The University of Edinburgh
Imperial College London
wellcome trust sanger institute
London School of Hygiene & Tropical Medicine
Public Health England
The Hepatitis C Trust
Medivir
MERCK Be well
GILEAD
Janssen
United Therapeutics Corporation
Conatus Pharmaceuticals
oncimmune

HCV Research UK

MRC Medical Research Foundation
MRC Medical Research Council