THE FORUM
For Collaborative Research℠

Updates from NASH Biomarkers Consortia

LITMUS

Quentin Anstee, Newcastle University
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Berkeley School of Public Health

Collaboration in Action: The Investigative Medicines Initiative (IMI2)

Liver Investigation: Testing Marker Utility in Steatohepatitis

Liver Forum #8, Paris, April 2018

Prof Quentin M. Anstee PhD, FRCP

Project Coordinator (Newcastle University, UK)

Dr Julia Brosnan PhD

Project Lead (Pfizer, USA)

Disclosure Slide

Research Grant Funding

Abbvie, Allergan/Tobira, Astra Zenica, GlaxoSmithKline, Novartis Pharma AG, Pfizer Ltd., Vertex.

Active Research Collaborations (including research supported through the EU IMI2 LITMUS Consortium*)

Abbvie, Antaros Medical*, Allergan/Tobira, AstraZenica, Boehringer Ingelheim International GMBH*, Ellegaard Gottingen Minipigs AS*, Eli Lilly & Company Ltd.*, Exalenz Bioscience Ltd.*, Genfit SA*, GlaxoSmithKline, Intercept Pharma Europe Ltd.*, iXscient Ltd.*, Nordic Bioscience*, Novartis Pharma AG*, Novo Nordisk A/S*, One Way Liver Genomics SL*, Perspectum Diagnostics*, Pfizer Ltd.*, Sanofi-Aventis Deutschland GMBH*, SomaLogic Inc.*, Takeda Pharmaceuticals International SA*.

Consultancy

Abbott Laboratories, Acuitas Medical, Allergan/Tobira, E3Bio, Eli Lilly & Company Ltd., Galmed, Genfit SA, Gilead, Grunthal, Imperial Innovations, Intercept Pharma Europe Ltd., Inventiva, Janssen, Kenes, Madrigal, MedImmune, NewGene, NGMBio, Novartis, Pfizer Ltd., Raptor Pharma, Servier.

Speaker

Abbott Laboratories, Allergan/Tobira, BMS, Clinical Care Options, Falk, Genfit SA, Gilead.

Newcastle University

The Imperative for Biomarkers in NAFLD

An important paradox exists: a significant proportion of the population have NAFLD but only a minority progress to advanced liver disease or morbidity/mortality

The Imperative for Biomarkers in NAFLD

An important paradox exists: a significant proportion of the population have NAFLD but only a minority progress to advanced liver disease or morbidity/mortality

A lack of tractable non-invasive biomarkers has impeded the diagnosis, risk stratification and monitoring of patients and so many cases remain undiagnosed and present with advanced disease.

The lack of biomarkers has also hampered drug development and the conduct of clinical trials, which still depend on histological effect as an endpoint.

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LITMUS Concept

A goal-oriented, tri-partite collaboration is best placed to deliver a definitive and impartial evaluation of available and new biomarkers.

- **End-users of biomarker technologies**
    - Practicing clinicians with expertise in NAFLD
    - Pharmaceutical industry (EFPIA partners & Partners in Research);
- **Independent academics** with expertise in the evaluation of medical test/biomarker performance
- **Biomarker researchers and developers**
    - Academic
    - Commercial

LITMUS Concept

A goal-oriented, tri-partite collaboration is best placed to deliver a definitive and impartial evaluation of available and new biomarkers.

LITMUS will implement a robust 'technology-unbiased' platform and conduct the systematic study and validation of a broad range of non-invasive biomarkers and technologies relevant to NAFLD with reference to fully-adjudicated liver biopsy data.

- **LITMUS will align with the EMA/FDA accord for *Qualification of Biomarkers & Clinical Outcome Assessments***
- **Generate the requisite level of high-quality data to support biomarker validation and the evidence needed for regulatory qualification.**

LITMUS Concept

A goal-oriented, tri-partite collaboration is best placed to deliver a definitive and impartial evaluation of available and new biomarkers.

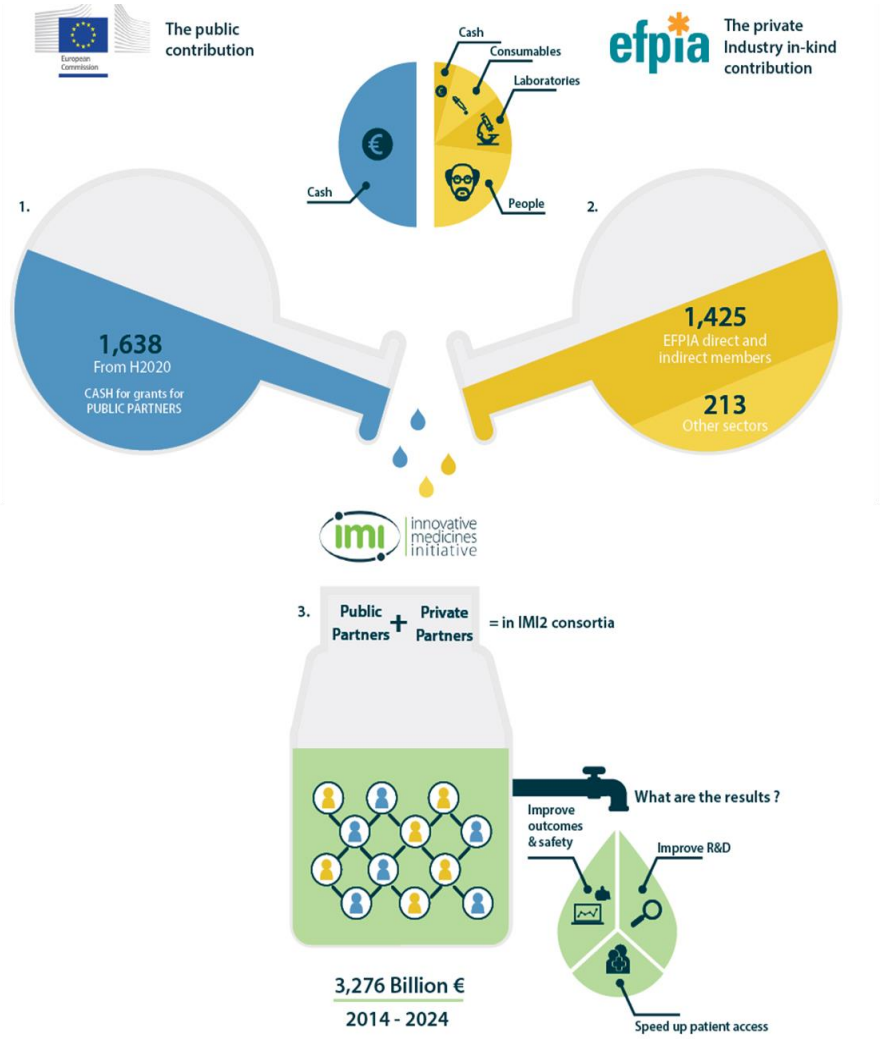
LITMUS will implement a robust 'technology-unbiased' platform and conduct the systematic study and validation of a broad range of non-invasive biomarkers and technologies relevant to NAFLD with reference to fully-adjudicated liver biopsy data.

Our ultimate goal is to establish a defined set of biomarkers that, singly or in combination, enable detection and monitoring of disease progression to and/or regression from NAFL through NASH to fibrosis and cirrhosis.

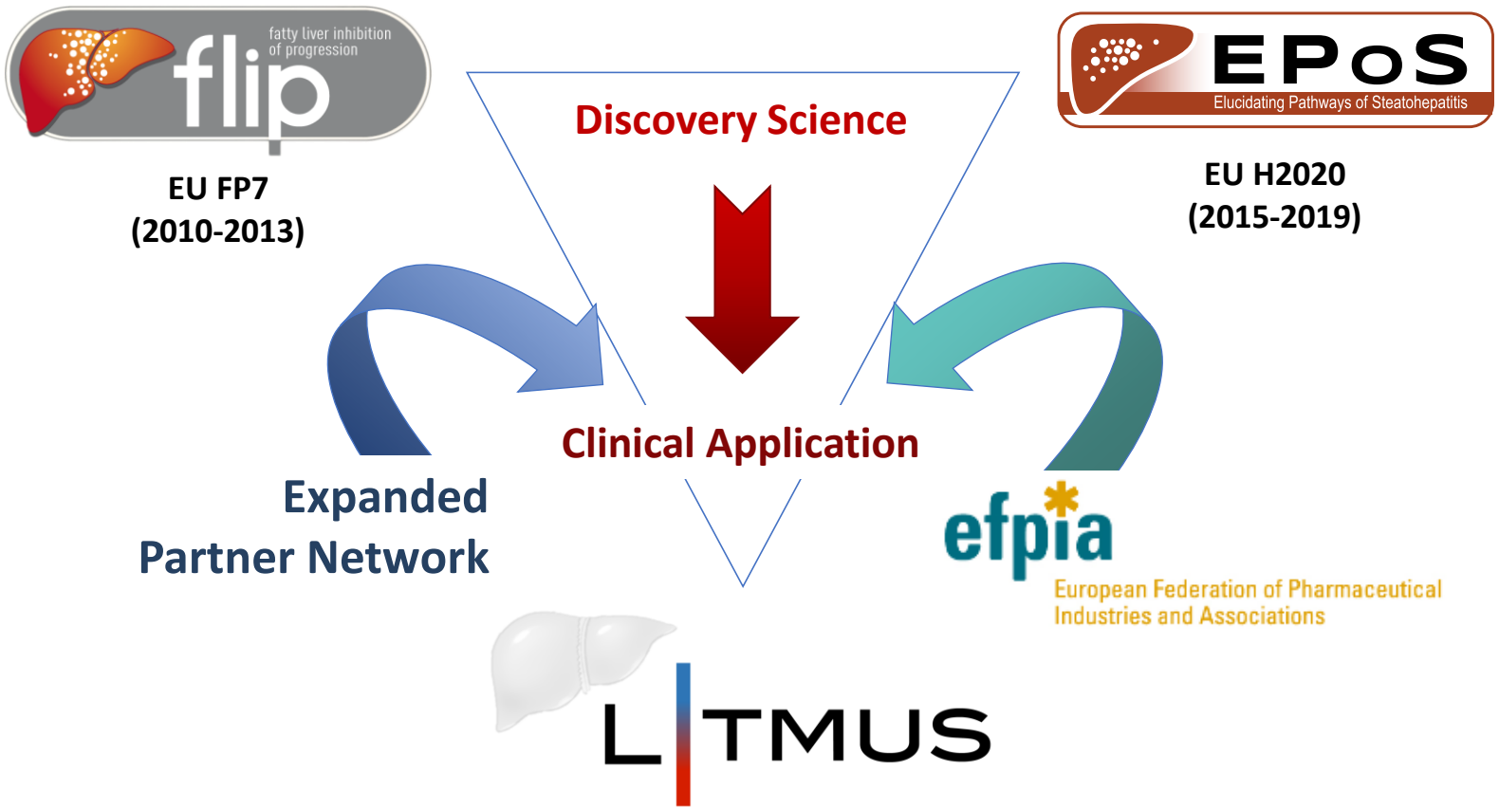
- To assist **drug development** and the conduct of clinical trials
- To enable the cost-effective management of NAFLD in **clinical practice**.

The Investigative Medicines Initiative (IMI2) Scheme

- Focus on unmet needs
- Non-competitive collaborative research
- Competitive Calls for proposals
- Pooling expertise, knowledge and resources, cross-fertilisation
- Developing incentives to address major unmet medical needs
- Providing a neutral trusted platform to align public and private interests



Strong Collaborative Foundations in Discovery Science

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Perspectum Diagnostics
Exalenz
Breathtaking Solutions

Liver Investigation: Testing Marker Utility in [illegible] (LITMUS)

FACTS & FIGURES

Start Date	01/11/2017
End Date	31/10/2022
Contributions	**€**
IMI Funding	15 797 881
EFPIA in kind	15 571 213
Other	1 103 310
Total Cost	32 472 404

PROJECT LINKS

Project website:
www.litmus-project.eu

Twitter:
@LITMUS_IMI

- **47 Partners***
  - 29 Academic,
  - 17 EFPIA/Industrial,
  - 1 Professional body
- **14 Countries for Clinical Recruitment**
  - UK, France, Germany, Italy, Switzerland, Netherlands, Austria, Luxembourg, Sweden, Finland, Greece, Spain, Portugal, USA
- **True Public-Private co-funding model**
  - Effective budget >€34 million
    (includes >€20 million 'cash' from EU & Industry)

* **Membership expanding due to addition of more industrial partnerships.**

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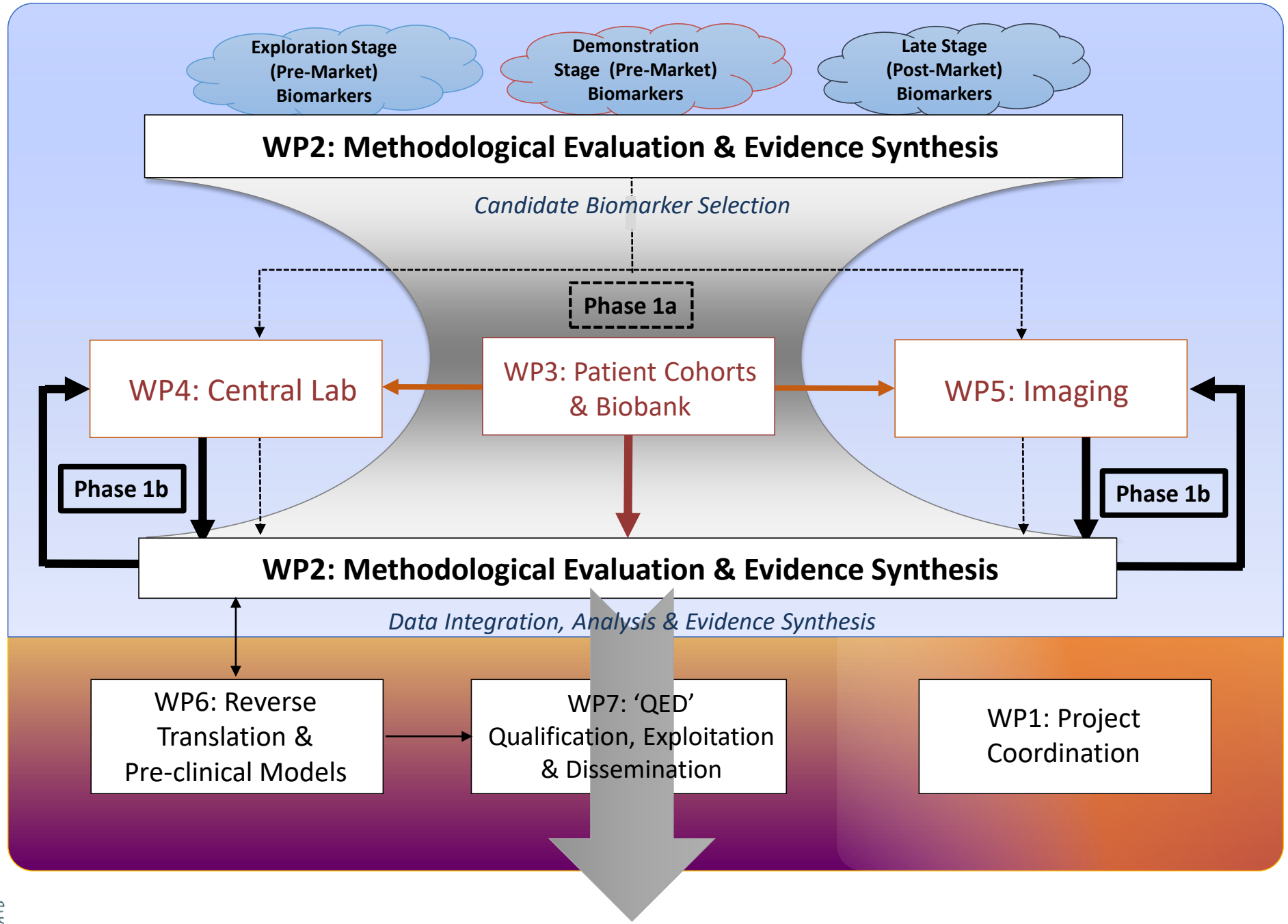

Validated Diagnostic, Prognostic & Dynamic Biomarkers

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LITMUS Work Package Partnerships

		Academic Lead	Industry Lead
WP1	Coordinator/Project Lead:	Quentin Anstee (UNEW)	Julia Brosnan (PFE); Kevin Duffin (LLY)
	Project Manager:	David Wenn (IXS)	
WP2	Analysis, Evaluation & Evidence Synthesis:	Patrick Bossuyt (AMC)	David Manner (LLY)
WP3	Recruitment/Registry: PROM: Biobank: Histopathology:	Quentin Anstee (UNEW); Vlad Ratziu (ICAN) Luke Vale (UNEW) Fay Betsou (IBBL) Pierre Bedossa (APHP); Dina Tiniakos (UNEW)	Remy Hanf (GNFT) Magdalena Balp (NOVA) - -
WP4	Central Labs: Protein/Collagen: Genetics/miRNA: Lipidomics: Metagenomics: Near-Patient Testing:	- Detlef Schuppan (UMCM) Ann Daly (UNEW) Tuulia Hyötyläinen (ORU) Karine Clement (ICAN) Andreas Geier (UKW)	Diana Leeming (NB) Jessica Ash (SOMA) Pierre Chaumat (GNFT); Melissa Miller (PFE) Pablo Ortiz Betes (OWL) - Melina Arazy (EXA)
WP5	Imaging:	Stephen Harrison (UOXF)	Theresa Tuthill (PFE)
WP6	Pre-Clinical Models:	Toni Vidal-Puig (UCAM)	Haiquin Hua (LLY)
WP7	Qualification, Exploitation & Dissemination (QED)	Vlad Ratziu (ICAN); Chris Day (UNEW)	Richard Torstenson (NOVO); Morten Karsdal (NB)
WP8	Ethics Lead:	Jörn Schattenberg (UMCM)	-

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LITMUS P ss

- Two-day Project Kick-Off Meeting
  - November 2017
  - Newcastle, UK
  - 128 delegates across all partners in attendance

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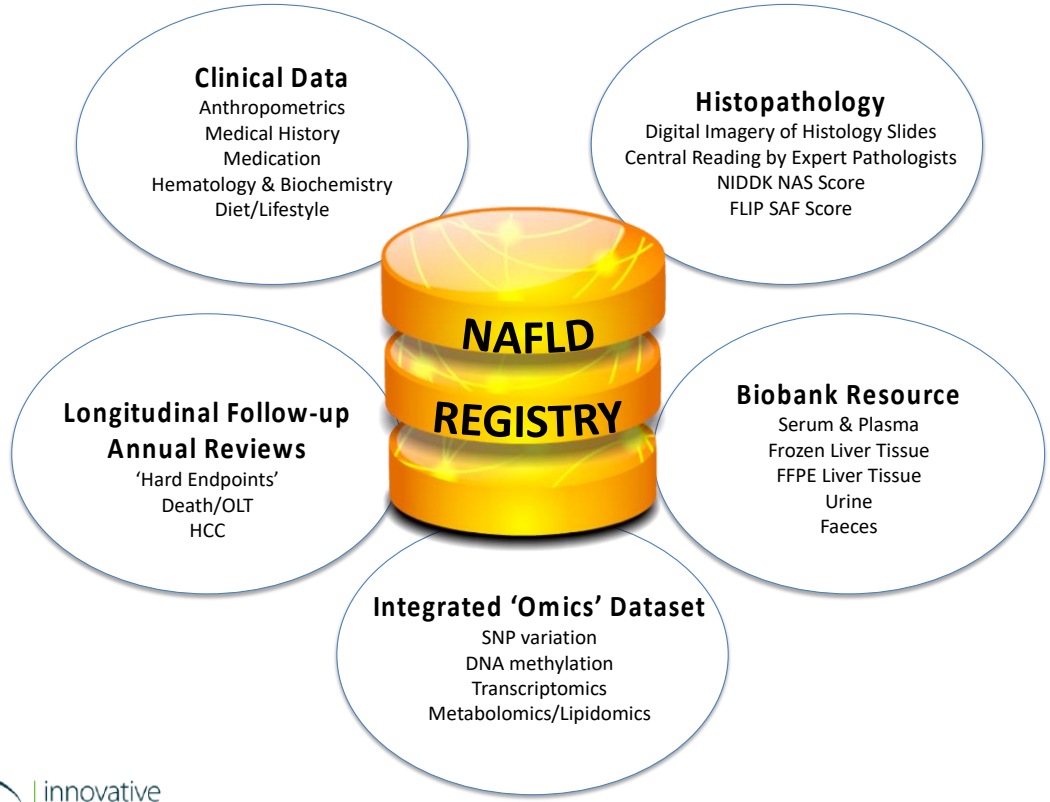
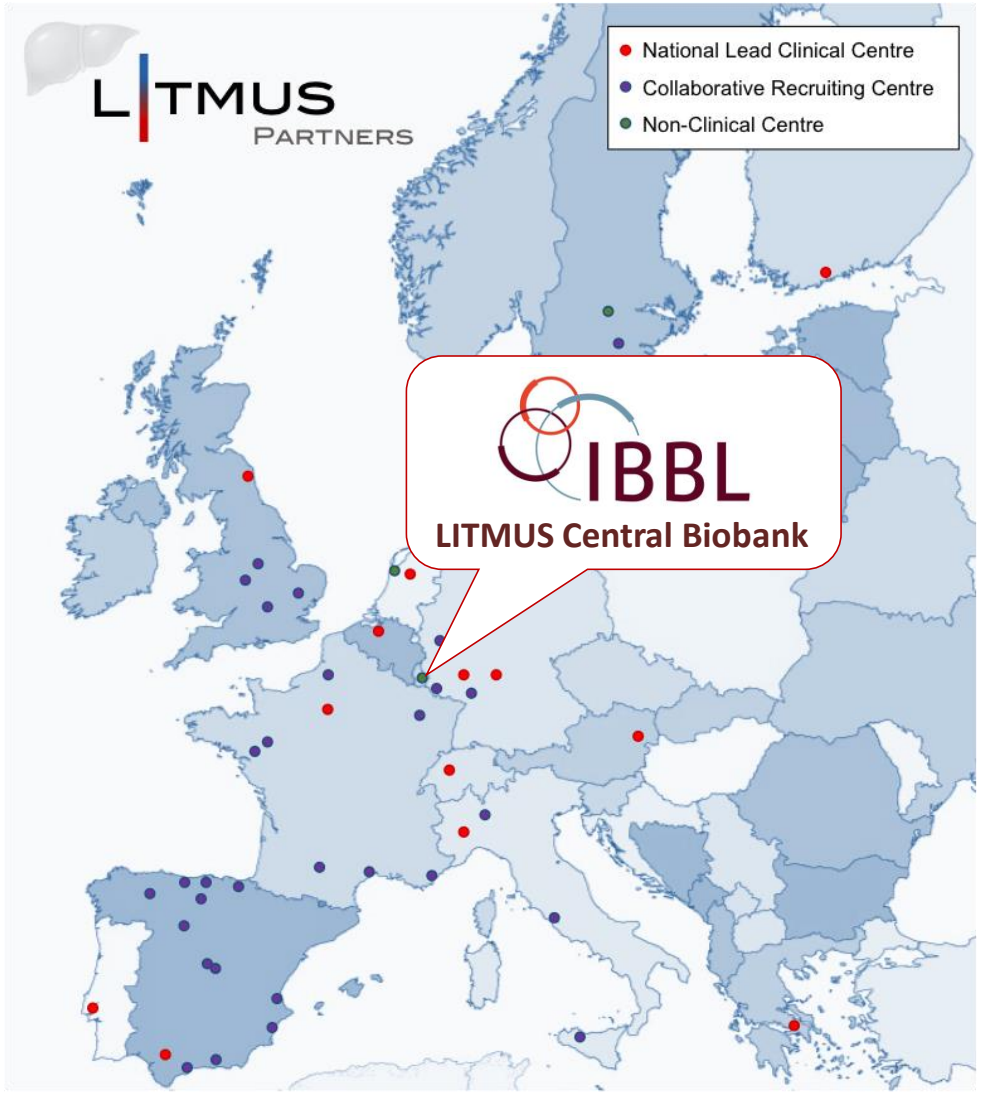
LITMUS Progress (Y1H1)

- ✓ Initiate LITMUS specific Ethics Applications across all sites.
- ✓ Inventory & Centralisation of existing Bioresources
- ✓ Upgrading the European NAFLD Registry Database





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LITMUS

The European NAFLD Registry

LITMUS (Liver Investigation: Testing Marker Utility in Steatohepatitis)

INVESTIGATOR HANDBOOK & LABORATORY MANUAL

Laboratory Manual Version: 1.0 (dated 26/02/2018)

Funders:

The *European NAFLD Registry* and *LITMUS consortium* are funded by the *Innovative Medicines Initiative* (IMI2) Program of the European Union (Grant Agreement 777377).

Newcastle University

8. Processing of Research Samples

NOTE: All samples must be handled in accordance with local hospital/clinic s
procedures for biological samples. Samples are to be collected after an overnight fast.

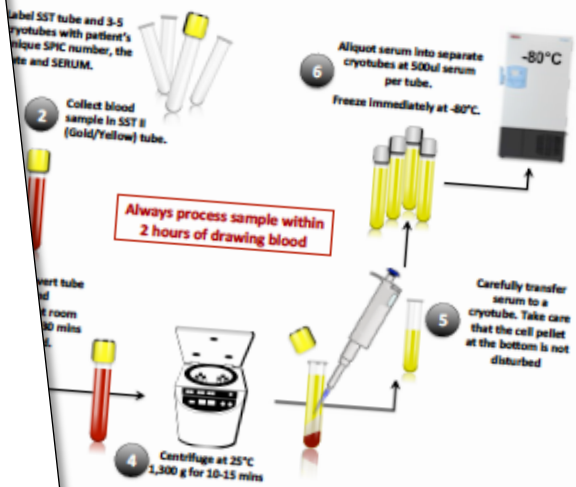
8.1. Serum Sample Preparation from SST II (Gold) tubes

ample/Test	Number & Type of Blood Sample Tubes	VISITS
rum – Biomarkers & Metabolomics	4 x 5ml (or 2 x 10ml) SST II tubes (GOLD Vacutainer)	Collected at Enrolment each Annual follow-up

of blood should be collected into BD serum separator (SST) tubes. The tubes sho
be mixed by carrying out five complete inversions, before leaving to coagulate
nt temperature for at least 30 minutes in a vertical position (ensure that samples a
kept at room temperature for longer than 2 hours*). After clotting is complete t
hould be centrifuged at approximately 1300 g for 10-15 minutes** setting t
ge to 25ºC. The serum should then be harvested into 500 µl - 1 ml aliquots (500
preferred) in appropriately labelled screw-cap polypropylene storage tubes. The
80°C.

sing within two hours of taking the sample is not possible, once the sample has clotted co
processed, ensure that the time the sample waited for processing is recorded.]
es horizontal (swing bucket centrifuge), 15 minutes fixed angle centrifuge)

of SST (clotted) tubes for Serum



arrange collection of batches of samples by courier for storage at the

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (IPAQ)

SPIC: ..... Date: ..... [IPAQ Page 1 of 5]

CHRONIC LIVER DISEASE QUESTIONNAIRE (CLDQ)

SPIC:

EPIC FOOD FREQUENCY QUESTIONNAIRE (EPIC-FFQ)

SPIC: ..... Date: ..... [EPIC-FFQ Page 1 of 11]

MEDITERRANEAN DIET SCORE (MDS)

SPIC: ..... Date: ..... [MDS Page 1 of 1]

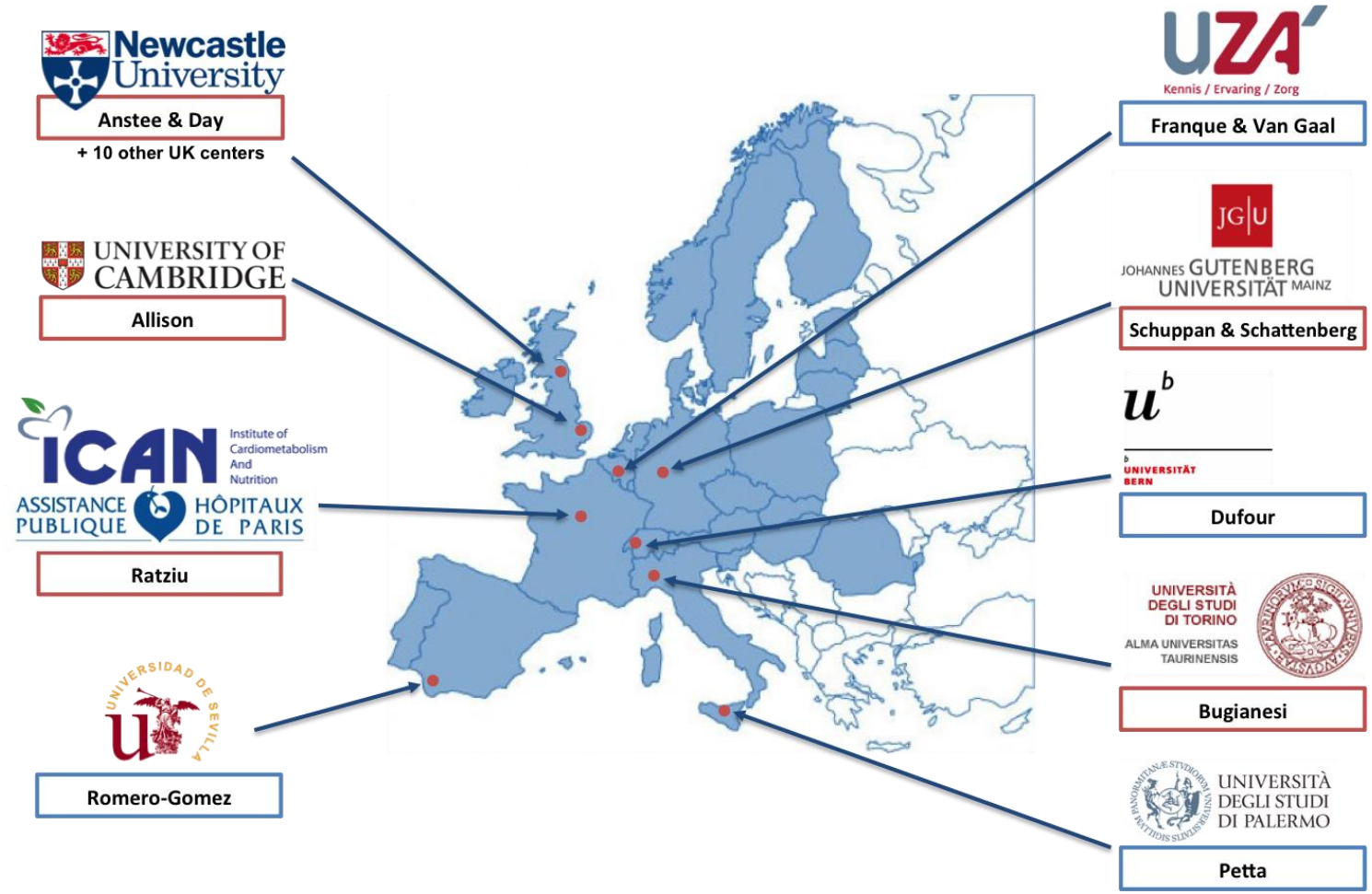
A Mediterranean dietary pattern ('Med diet') is typically one based on whole or minimally processed foods. It's rich in protective foods (fruits, vegetables, legumes, wholegrains, fish and olive oil) and low in adverse dietary factors (fast food, sugar-sweetened beverages, refined grain products and processed or energy-dense foods) with moderate red meat and alcohol intake.

Evidence shows **overall dietary pattern** (reflected in TOTAL SCORE) as well as **individual components** reflect risk; a higher score is associated with lower risk of CVD and all-cause mortality (BMJ 2008;337:a1344). During rehabilitation patient scores should ideally rise in response to dietary advice and support.

This tool can be used by health professionals with appropriate nutritional knowledge and competencies, such as Registered Dietitians (NICE, 2007, 2013). It can be used as both an *audit tool* and *as part of a dietary assessment* at baseline, end of programme and 1 year follow-up, along with assessment and advice for weight management, salt intake and eating behaviours. For information on complete requirements for dietary assessments and advice, please refer to the latest NICE/Joint British Societies guidelines (BACPR, 2012. The BACPR Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation, 2nd Ed.).

	Question	Yes	No	Nutritional issue to discuss in response
1.	Is olive oil the main culinary fat used?			**Choosing Healthier Fats** Olive oil is high in monounsaturated fat. Using unsaturated fats instead of saturated fats in cooking and preparing food is advisable.
2.	Are ≥ 4 tablespoons of olive oil used each day?			**Healthy fats are better than very low fat** Med diet is more beneficial than a very low fat diet in prevention of CVD. So replacing saturated with unsaturated fat is better than replacing it with carbohydrates or protein.
3.	Are ≥ 2 servings (of 200g each) of vegetables eaten each day?			**Eat plenty of fruits and vegetables** Eating a wide variety of fruit and vegetables every day helps ensure adequate intake of many vitamins, minerals, phytochemicals and fibre. Studies have shown that eating plenty of these foods is protective for CVD and cancer.
4.	Are ≥ 3 servings of fruit (of 80g each) eaten each day?			
5.	Is < 1 serving (100-150g) of red meat/ hamburgers/ other meat products eaten each day?			**Choose lean meats and consider cooking methods** Red and processed meats are high in saturated fat, can be high in salt and are best replaced with white meat or fish or vegetarian sources of protein. Grill or roast without fat, casserole or stir fry.
6.	Is < 1 serving (12g) of butter, margarine or cream eaten each day?			**Keep saturated fat low** These foods are high in saturated fat which can increase your blood cholesterol level. Choose plant-based or reduced-fat alternatives.
7.	Is < 1 serving (330ml) of sweet or sugar sweetened carbonated beverages consumed each day?			Excessive consumption of sugar-sweetened beverages can worsen many risk factors for CVD: keep consumption to < 1/day.
8.	Are ≥ 3 glasses (of 125ml) of wine consumed each week?			**Moderate alcohol intake with meals** While this does have some protective effect but ***there is no evidence that non-drinkers should take up drinking alcohol.***
9.	Are ≥ 3 servings (of 150g) of legumes consumed each week?			**Include soluble fibre** These foods are high in soluble fibre and other useful nutrients. Regular consumption is advisable for raised cholesterol.
10.	Are ≥ 3 servings of fish (100-150g) or seafood (200g) eaten each week?			**Eat more oily and white fish** Oily fish is an excellent source of essential omega-3 fats. White fish is very low in saturated fat.
11.	Is < 3 servings of commercial sweets/pastries eaten each week?			**Eat less processed food** These foods are usually high in saturated fat, salt or sugar and often contain trans fats. Replacing these with healthy snacks such as fruit or unsalted nuts is beneficial.
12.	Is ≥ 1 serving (of 30g) of nuts consumed each week?			**Snack on modest servings of unsalted nuts** Nuts are rich in unsaturated fat, phytosterols, fibre, vitamin E and iron, **e.g. walnuts, almonds, hazelnuts**
13.	Is chicken, turkey or rabbit routinely eaten instead of veal, pork, hamburger			'White meat' choices are lower in saturated fat. Remove the skin and consider your cooking method.

LITMUS Progress (Y1H1)



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Geier

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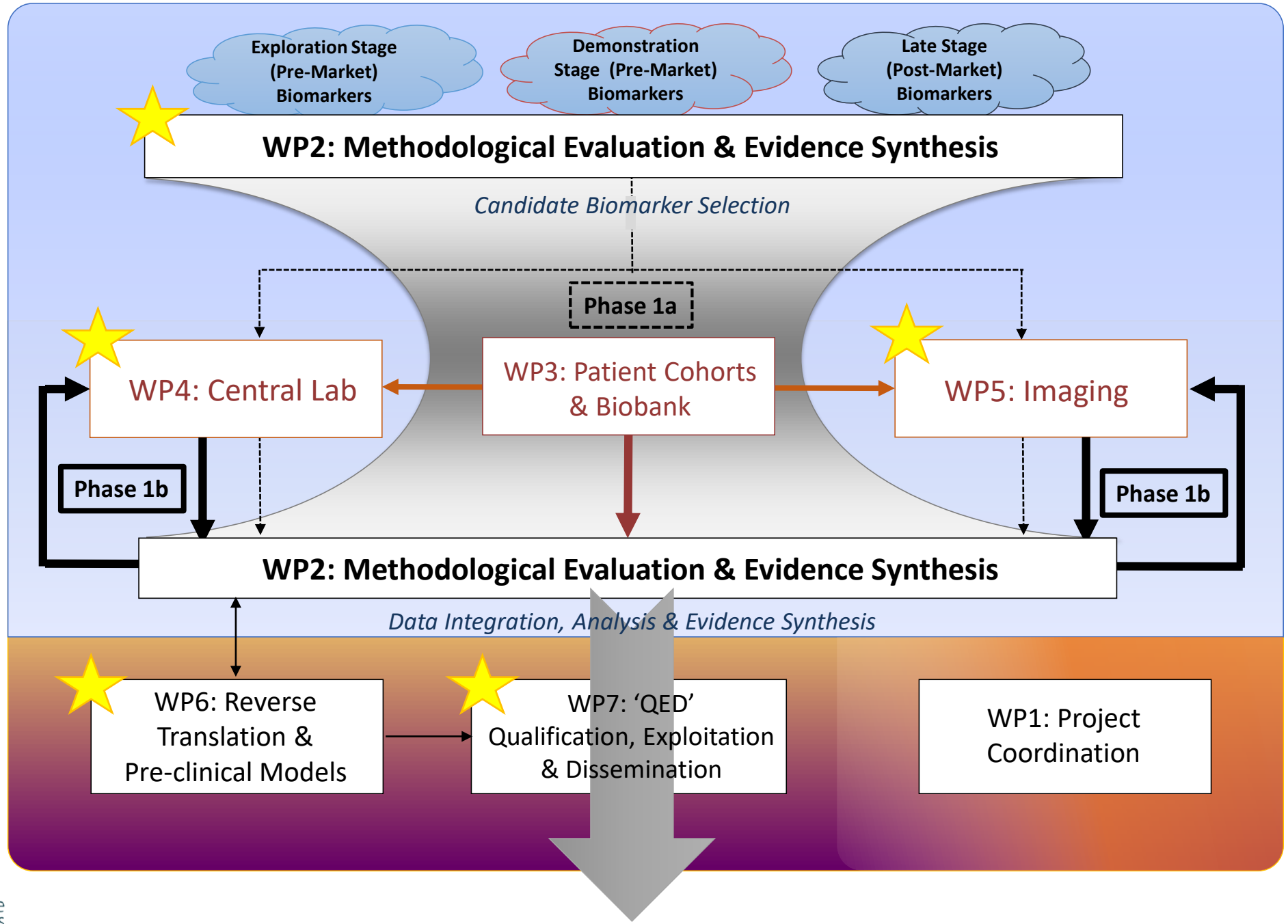
Miele

Prospective Recruitment & Follow-up of Existing Patients in the European NAFLD Registry already ongoing throughout the LITMUS set-up process

EPoS
Elucidating Pathways of Steatohepatitis



Validated Diagnostic, Prognostic & Dynamic Biomarkers

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Conclusions

- LITMUS is a focused, pragmatic and goal-oriented programme, founded on a strong track-record of NAFLD research, that addresses the pressing need for validated non-invasive biomarkers.
- The LITMUS ambition is to make a fundamental difference to the way NAFLD/NASH is diagnosed, clinical trials are conducted and the way patients are managed.

LITMUS has the demonstrable capacity to provide much needed clarity on biomarker validity *at scale and pace* and thus deliver a step change in drug development and the care of patients with NAFLD

- Following project kick-off in November 2017, LITMUS has made rapid progress across both the clinical platform and the evaluation platform – establishing a sound foundation for the project.

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EASL
European Association for the Study of the Liver
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The LITMUS project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 777377. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

www.litmus-project.eu

www.imi.europa.eu

HORIZON 2020

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