Collaboration in Action: The Investigative Medicines Initiative (IMI2)

Liver Investigation: Testing Marker Utility in Steatohepatitis

Paris NASH Symposium, France, July 7th 2017

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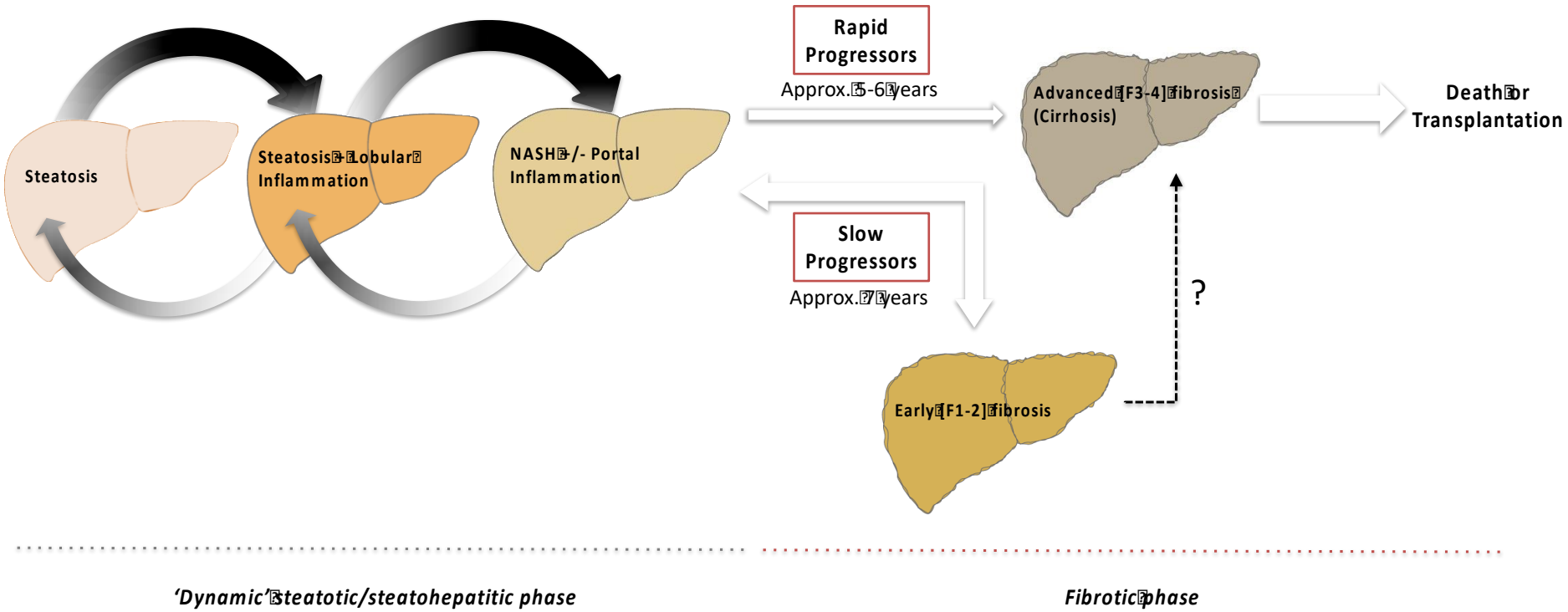
Project Lead (Pfizer, USA)

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.

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,*** in compliance with:
  - EMA CHMP *Guidance on Qualification of Novel Methodologies for Drug Development;*
  - FDA *510(k)/PMA pathway* or *Drug Development Tools (DDT) Qualification Program*;
- **Generate the requisite level of high-quality data to support biomarker validation and the evidence needed for regulatory qualification.**

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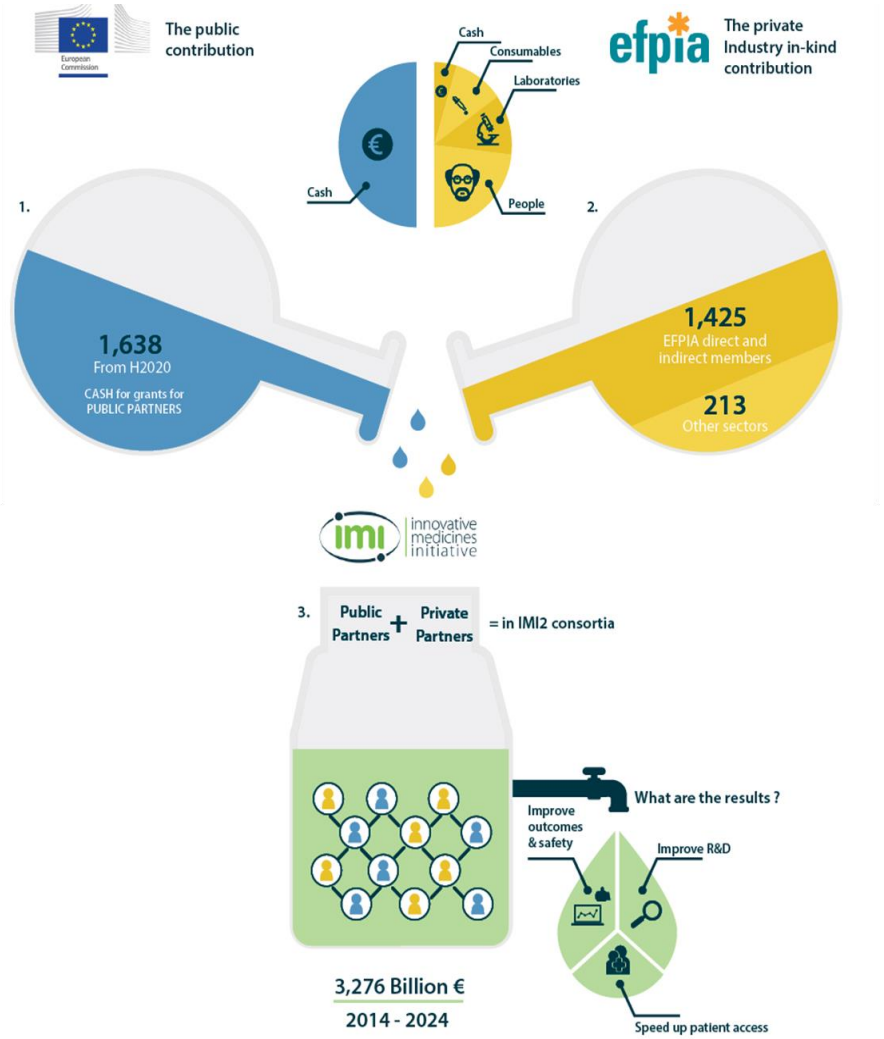
Our ultimate goal is to establish a defined set of biomarkers that, singly or in combination, enable detection and monitoring of disease progression to and/or regression from NAFL through NASH to fibrosis and cirrhosis.

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

The Innovative Medicine 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



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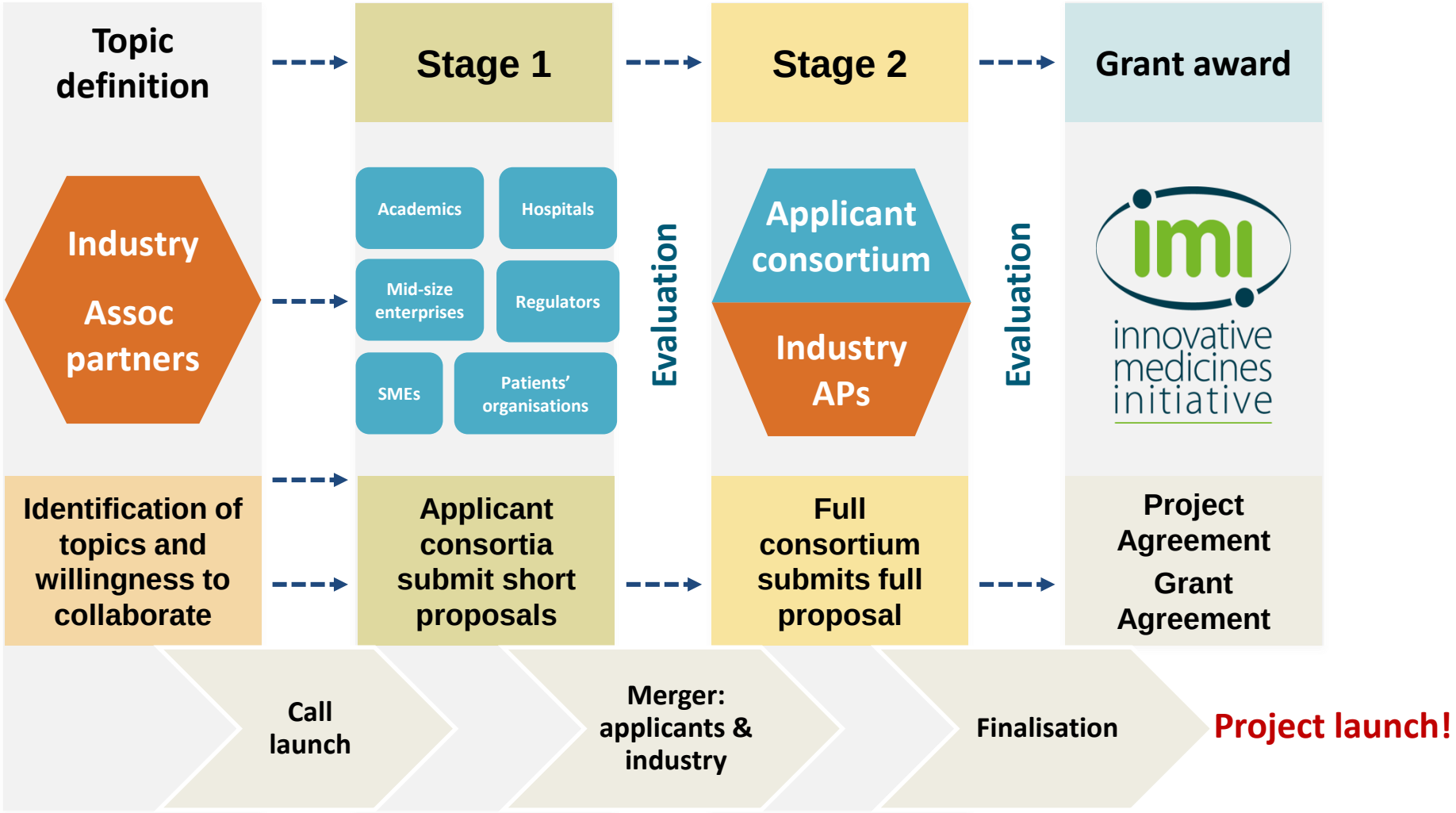
European Commission

Typical IMI2 Two-Stage Call Process



LITMUS Concept

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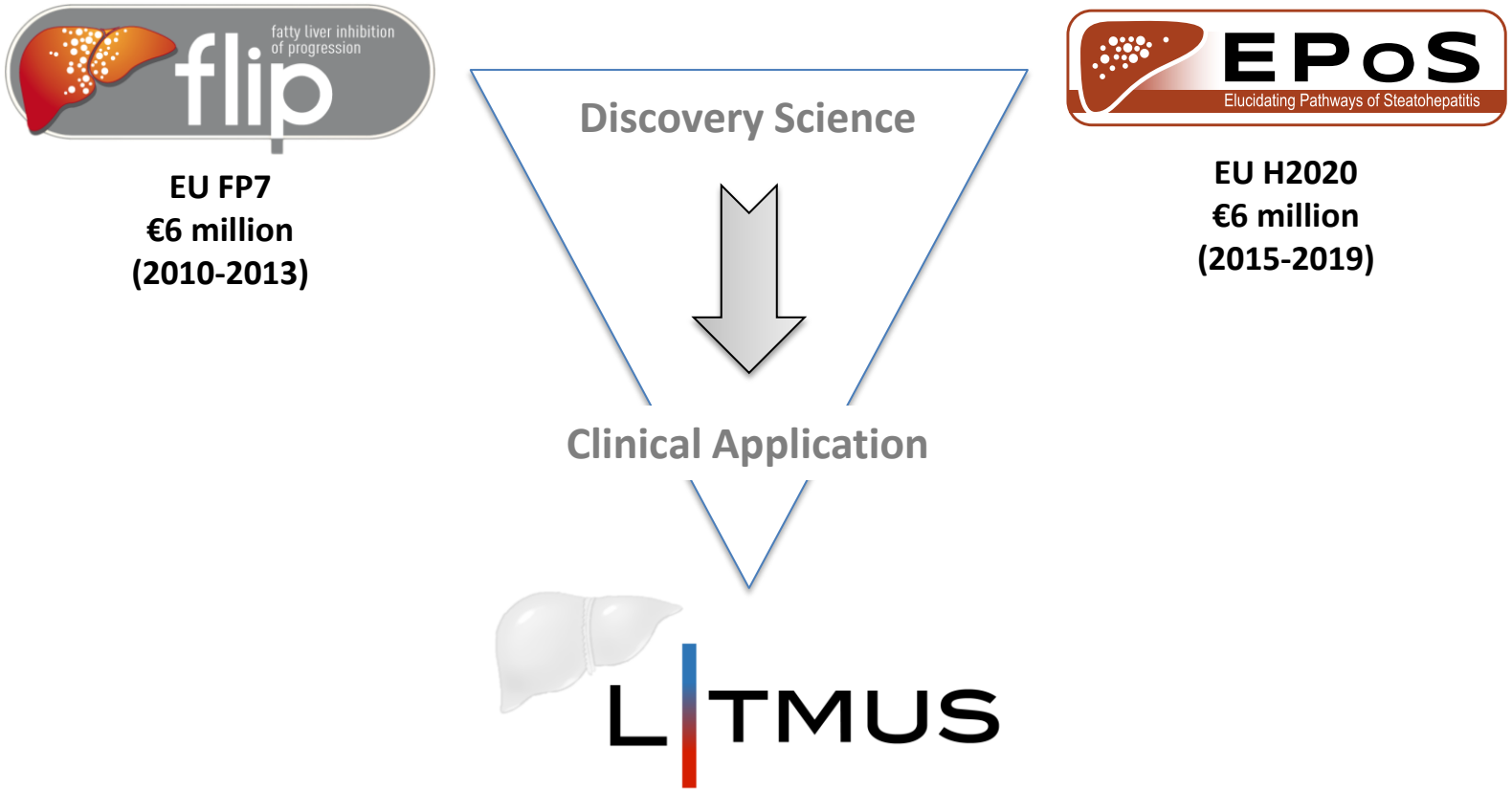
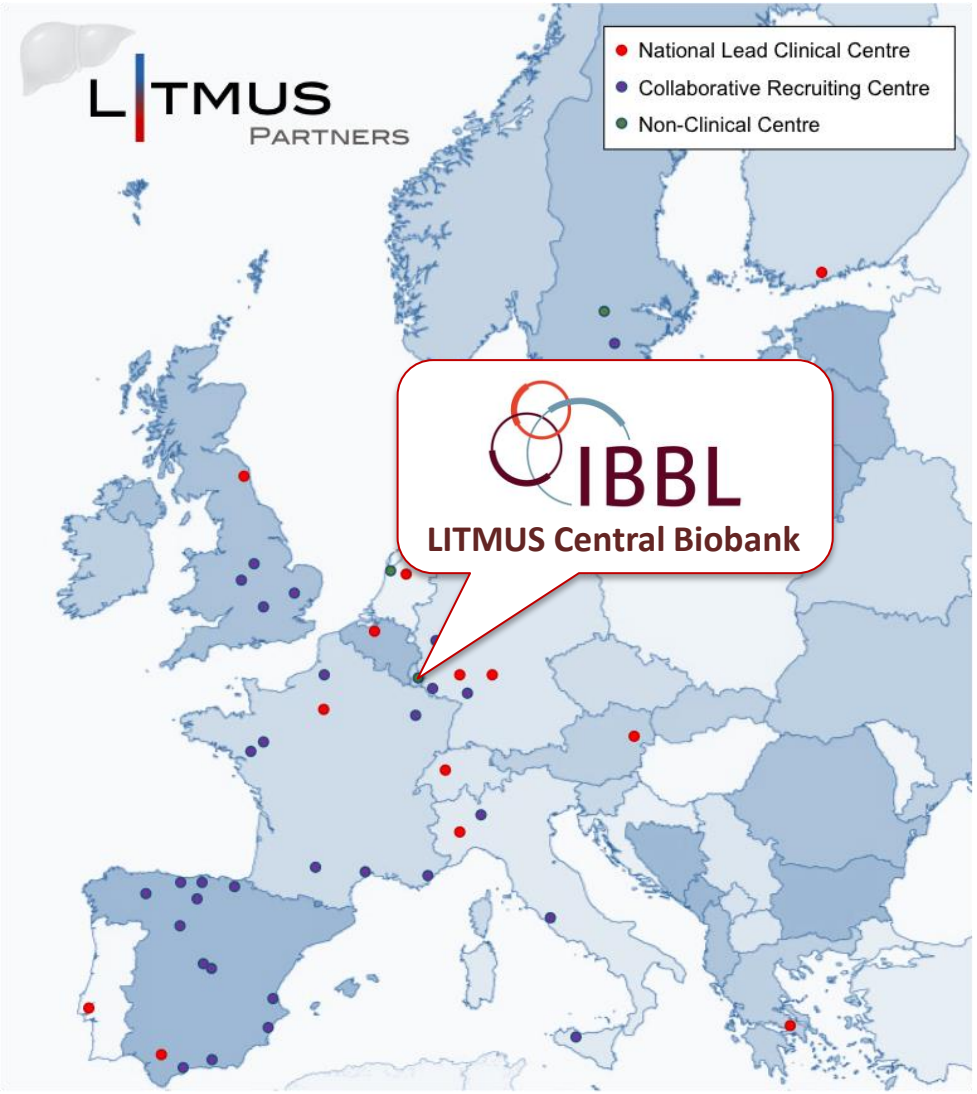
- **End-users of biomarker technologies**
  - Practicing clinicians with expertise in NAFLD
  - Pharmaceutical industry (EFPIA partners & Partners in Research);
- **Independent academics** with expertise in the evaluation of medical test/biomarker performance
- **Biomarker researchers and developers**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

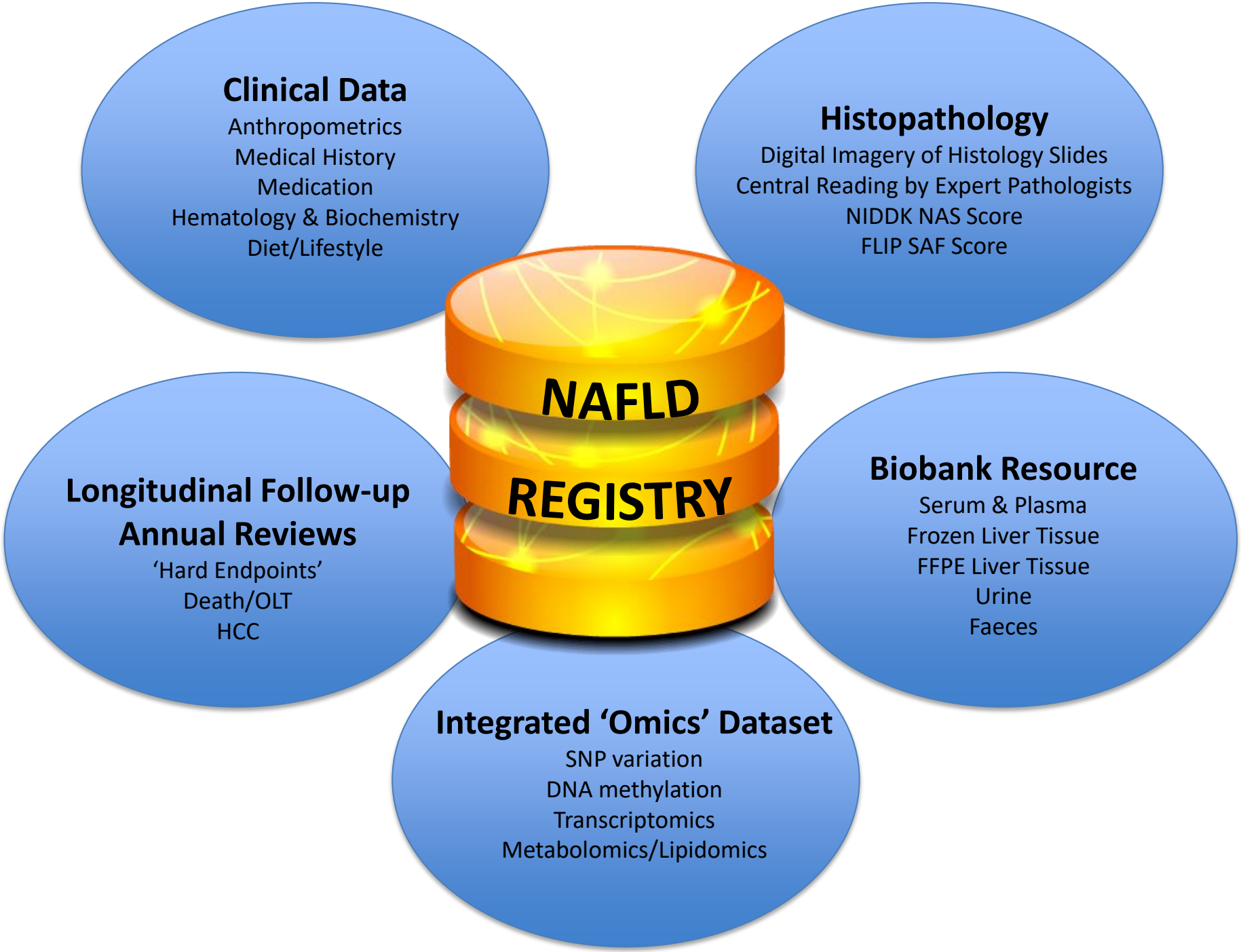
Strong Collaborative Foundations in Discovery Science



- Clinical recruitment to use a ‘hub and spoke’ model
  - National ‘hub’ centre(s) with feeding ‘spoke sites’
  - Performance management for recruitment
    - Quentin Anstee (UNEW) – UK
    - Vlad Ratziu (ICAN) – France
    - Jorn Schattenberg (UMC) – Germany
    - Andreas Geier (UHW) – Germany
    - Jean-Francois Dufour (UBE) – Switzerland
    - Michael Trauner (MUV) - Austria
    - Sven Franque (UZA) - Belgium
    - Elisabetta Bugianesi (UNITO) – Italy
    - Manuel Romero-Gomez (SAS) – Spain
    - Helena Cortez-Pinto (FML) – Portugal
    - Mattias Ekstedt (LIU) – Sweden
    - Hannele Yki-Jarvinen (UHEL) – Finland
    - Van Mil (UMCU) – Netherlands
    - George Papatheodoridis (NKUoA) – Greece



Additional Links to initiate a ‘Global NAFLD Network’ with USA (Harrison and Sanyal)



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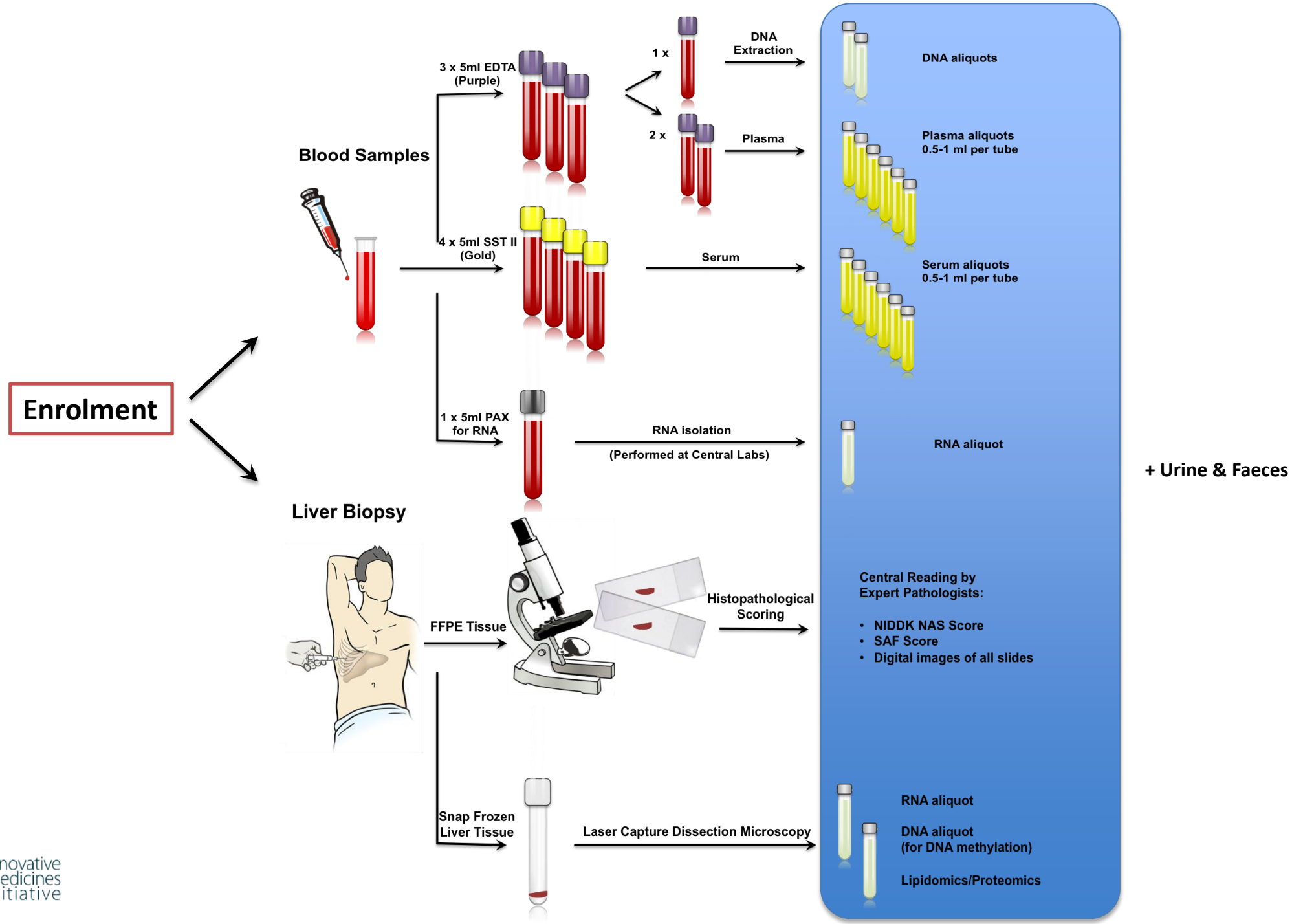
Enrolment
Blood Samples
3 x 5ml EDTA (Purple)
1 x
DNA Extraction
DNA aliquots
2 x
Plasma
Plasma aliquots 0.5-1 ml per tube
4 x 5ml SST II (Gold)
Serum
Serum aliquots 0.5-1 ml per tube
1 x 5ml PAX for RNA
RNA isolation
(Performed at Central Labs)
RNA aliquot
Liver Biopsy
FFPE Tissue
Histopathological Scoring
Central Reading by Expert Pathologists:
• NIDDK NAS Score
• SAF Score
• Digital images of all slides
Snap Frozen Liver Tissue
Laser Capture Dissection Microscopy
RNA aliquot
DNA aliquot (for DNA methylation)
Lipidomics/Proteomics
+ Urine & Faeces

Work Package Leaders & Key Partners

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

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 offers the promise of a decisive advance in NAFLD biomarker development and regulatory qualification and will thus facilitate therapeutics discovery and support the targeting of medical care to those at greatest risk.

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


EASL
European Association for the Study of the Liver
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HÔPITAUX UNIVERSITAIRES PARIS NORD VAL DE SEINE
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TOWARDS BETTER MEDICINE
ELLEGAARD
GÖTTINGEN MINIPIGS
UNIKLINIK RWTH AACHEN
ICAN
Institute of Cardiometabolism And Nutrition
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The University of Nottingham
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UNIVERSIDAD DE SEVILLA
UNIVERSITY OF CAMBRIDGE
owl
SANOFI
Newcastle University
UZA
Kennis / Ervaring / Zorg
National and Kapodistrian UNIVERSITY OF ATHENS
Pfizer
MEDICAL UNIVERSITY OF VIENNA
Boehringer Ingelheim
Takeda
LINKÖPING UNIVERSITY
Intercept
VCU Medical Center
UNIVERSITÀ DEGLI STUDI DI MILANO
UNIVERSITY OF OXFORD
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