Title: Recent Advances in the treatment of decompensated cirrhosis and acute-on-chronic liver failure (ACLF)

SUPPLEMENTARY MATERIAL

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SUPPLEMENTARY TABLE 1: Standard therapies

Complication of cirrhosis		Non-acute decompensation	Acute decompensation	ACLF
Hepatic encephalopathy		lactulose rifaximin BCAA, nutritional intervention	lactulose i.v. LOLA rifaximin+ BCAA+ nutritional intervention+	lactulose i.v. LOLA ALS (e.g MARS)
GI-bleeding		NSBB (prophylaxis) endoscopy (EVL) vasoconstrictors TIPS	endoscopy (EVL) vasoconstrictors TIPS	endoscopy (EVL) vasoconstrictors TIPS
Tense Ascites	**Responsive ascites**	nutritional intervention diuretics,	nutritional intervention* diuretics*,	nutritional intervention* albumin
	Recidivant ascites	diuretics TIPS albumin for LVP long-term albumin	TIPS albumin for LVP long-term albumin^{+}	TIPS albumin long-term albumin^{+}
	Refractory ascites	TIPS albumin for LVP long-term albumin	TIPS albumin for LVP long-term albumin^{+}	TIPS albumin RRT
SBP		cephalosporins albumin (d1/d3) norfloxacin^{+}	cephalosporins albumin (d1/d3) norfloxacin (prophylaxis)$^{+}$	broad-band antibiotics albumin (d1 and d3) norfloxacin (prophylaxis)$^{+}$
Non-SBP infection		antibiotics according to site of infection	antibiotics according to site of infection	antibiotics according to site of infection albumin
Alcohol-related hepatitis		steroids$^{\#}$	steroids$^{\#}$	steroids$^{\#}$
Reactivation of viral hepatitis		tenofovir	tenofovir	tenofovir (steroids)
AKI		stop nephrotoxic drugs albumin for 48h	stop nephrotoxic drugs albumin for 48h	stop nephrotoxic drugs albumin for 48h
HRS		albumin terlipressin	albumin terlipressin	albumin terlipressin (except for ACLF III)

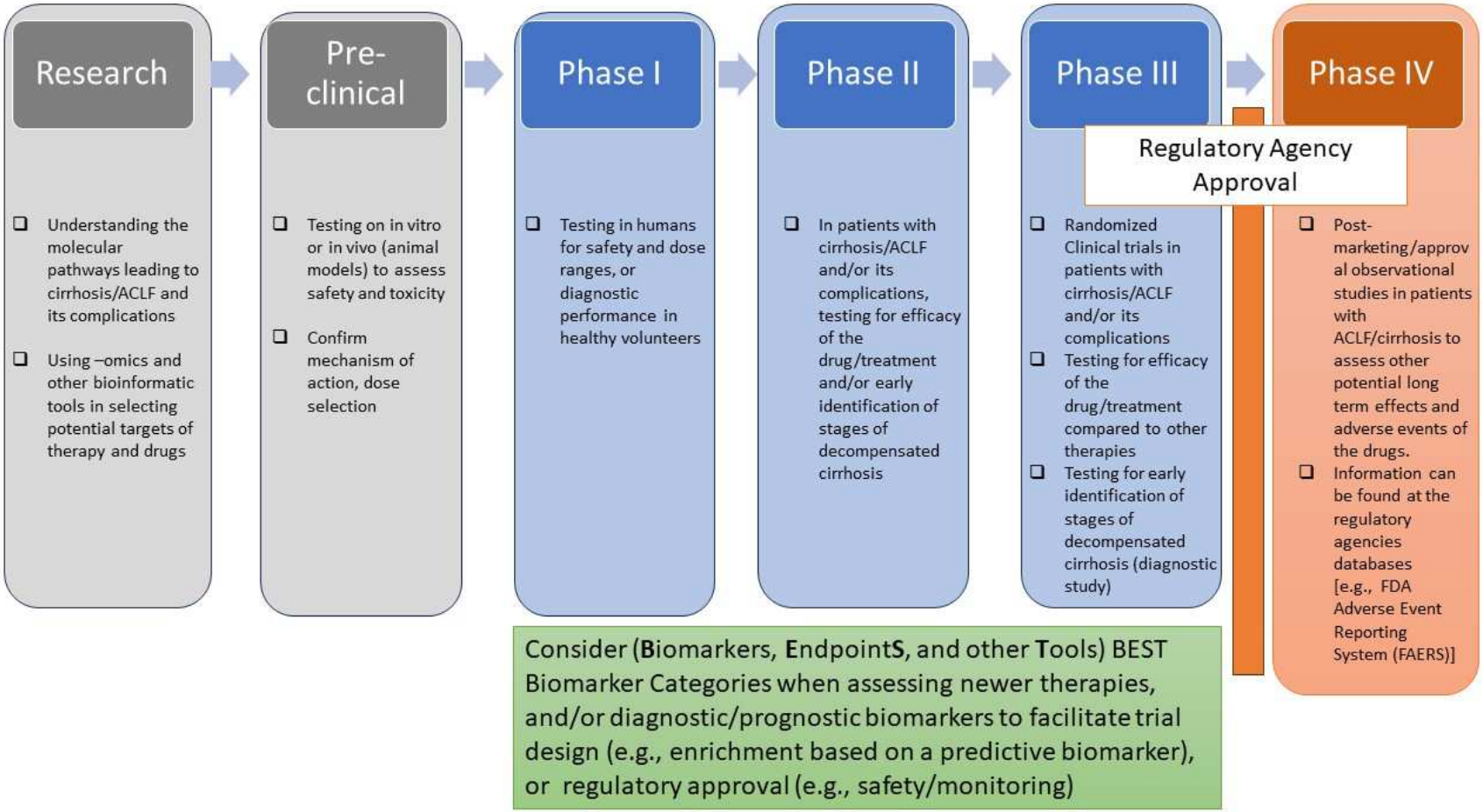
* effect is expected in long-term; $^{+}$ at discharge; $^{\#}$ according to Maddrey DF (Biggins et al. Hepatology. 2021 Aug;74(2):1014-1048; de Franchis et al. J Hepatol. 2022 Apr;76(4):959-974; EASL. J Hepatol. 2018 Aug;69(2):406-460; EASL. J Hepatol. 2023 Aug;79(2):461-491)

Abbreviations: AKI: acute kidney injury, HRS: hepatorenal syndrome, TIPS: transjugular portosystemic shunt; EVL: endoscopic variceal ligation; LVP: large volume paracentesis: d: day; ACLF: acute-on-chronic liver failure SBP: spontaneous bacterial peritonisis; GI: gastrointestinal: BCAA: Branched-chain amino acids; LOLA: l-Ornithine l-Aspartate; ALS: artificial liver support: MARS: Molecular adsorbent recirculating system; NSBB: non-selective beta blockers

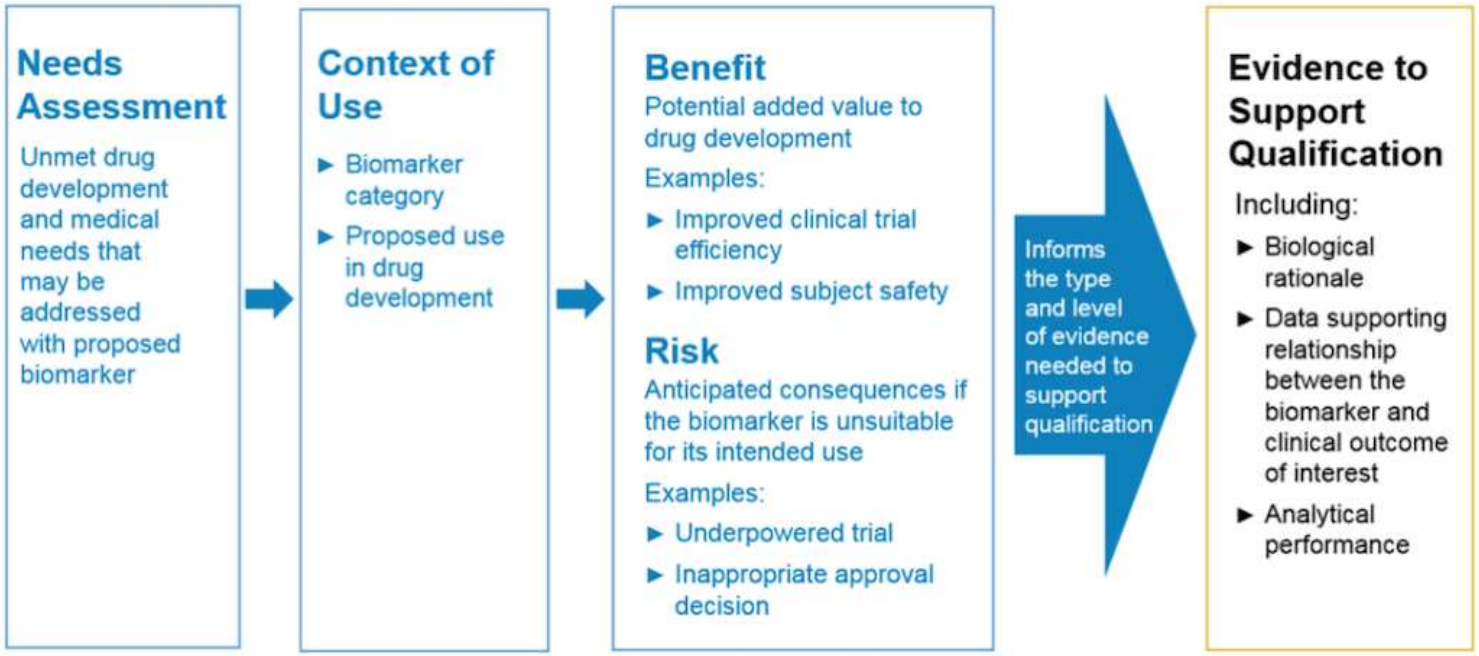
SUPPLEMENTARY TABLE 2. Example biomarker

	Description	Examples	
Biomarker name	Specific analyte (e.g., fibronogen), anatomic feature (e.g., resistive index), physiological characteristic (e.g., hepatic pressure gradient)	Neutrophil gelatinase-associated lipocalin	Alanine aminotransferase
Acronym	---	NGAL	ALT
Unique identifier (if applicable)	Formal chemical name or, if listed in a library or other resource, the correct name or unique identifier, referencing the resource and version. E.g. UniProt (http://uniprot.org/) HUGO Gene Nomenclature Committee (http://genenames.org), Protein Data Bank (http://rcsb.org/pdb/home/home.do), or Enzyme Commission (http://enzyme.expasy.org)	P80188	EC 2.6.1.2
Source	urine, biopsy, imaging, functional studies	Urinary	Serum
Type	molecular, histologic, radiographic, digital, or physiologic	Molecular	Molecular
Biological plausibility	Brief summary of the biological, physiological, or pathological pathway for the association of the biomarker with ACLF and its intended use. This information specifies how multiple biomarkers may interplay as part of a common use (e.g., shared biochemical pathways leading to a common biologic or clinical phenotype)	Neutrophil gelatinase-associated lipocalin (NGAL)is upregulated in experimental models of liver injury and cultured hepatocytes as a result of injury by toxins or proinflammatory cytokines, particularly interleukin-6. Ariza et al. found that NGAL was a marker of ACLF and prognosis correlating with liver failure, systemic inflammation and overexpression of LCN2 gene in ACLF. J Hepatol. 2016 Jul;65(1):57-65	ALT catalyses the transfer of an amino group from L-alanine to α-ketoglutarate, the products of this reversible transamination reaction being pyruvate and L-glutamate. In liver damage, it is released from hepatocyte injury into the circulation.
Measurement method	Description of method used to measure the biomarker to enable comparison across studies, e.g., ELISA	ELISA	spectrophotometric detection
Units of measurement	---	Mcg/gm creatinine	International Units/L
Point of care access/use?		No	Yes

Supplementary Figure 1. . Drug discovery and development processes with a potential to benefit from biomarkers in different clinical phases



Supplementary Figure 2. The suggested biomarker validation approach. Draft guidance. Food and Drug Administration in 2018. Available at: https://www.fda.gov/media/119271/download .



Supplementary Figure 3. The evidentiary framework was drafted by the Food and Drug Administration when determining the type and level of evidence sufficient to support the qualification of a biomarker. Available at: https://www.fda.gov/media/119271/download