Diseases to Watch

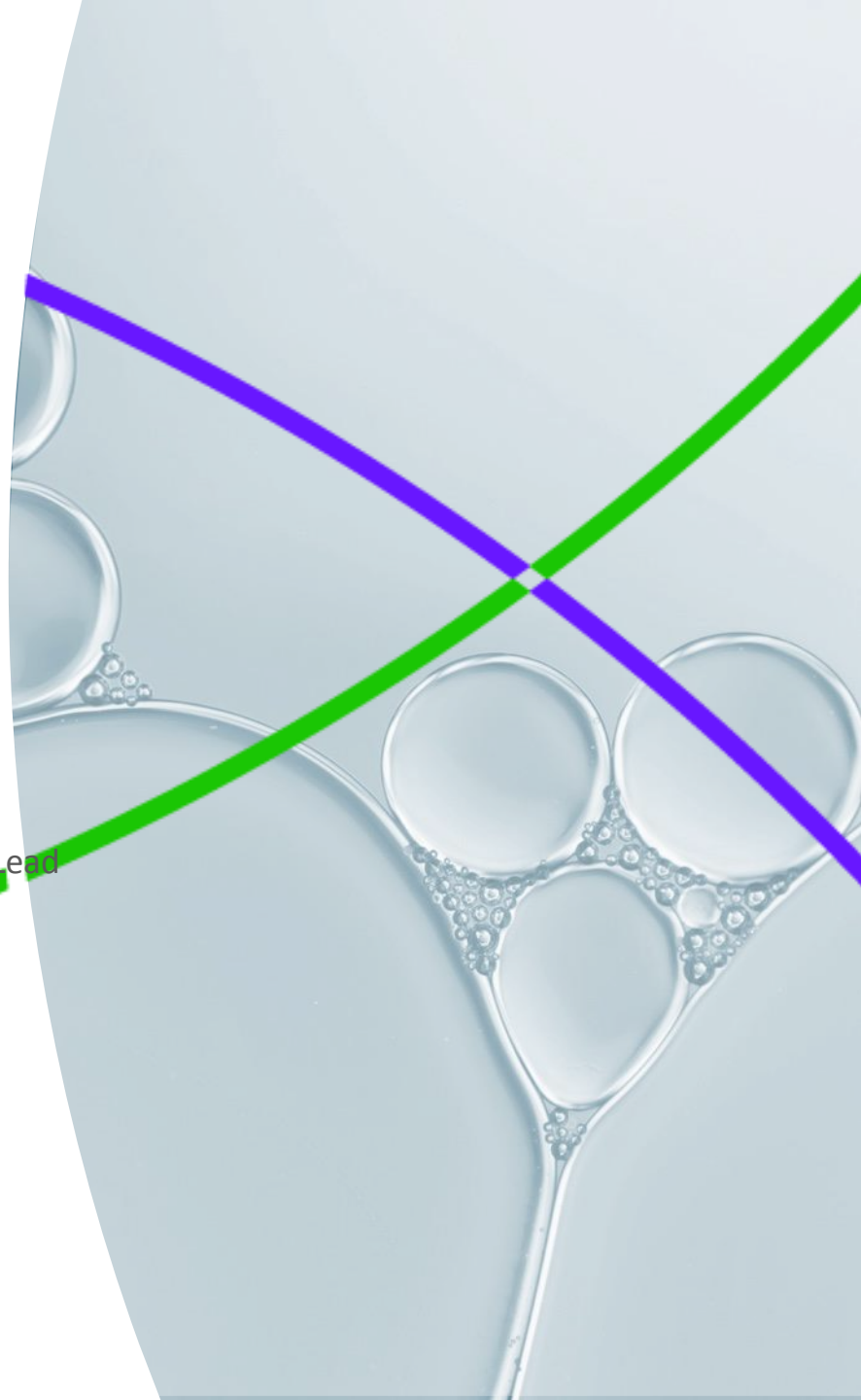
Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-alcoholic steatohepatitis (NASH)

- **Prevalence and Symptoms**
- **Risk Factors and Potential treatments**
- **Target identification for NASH**

Robert Poolman
Director of Preclinical Products

Carolyn Finch
Solution Scientist Team Lead

August 2018



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Featured Speakers

Dr. Robert Poolman
Director of Preclinical Products
Clarivate Analytics

Carolyn Finch
Solution Scientist Team Lead
Clarivate Analytics

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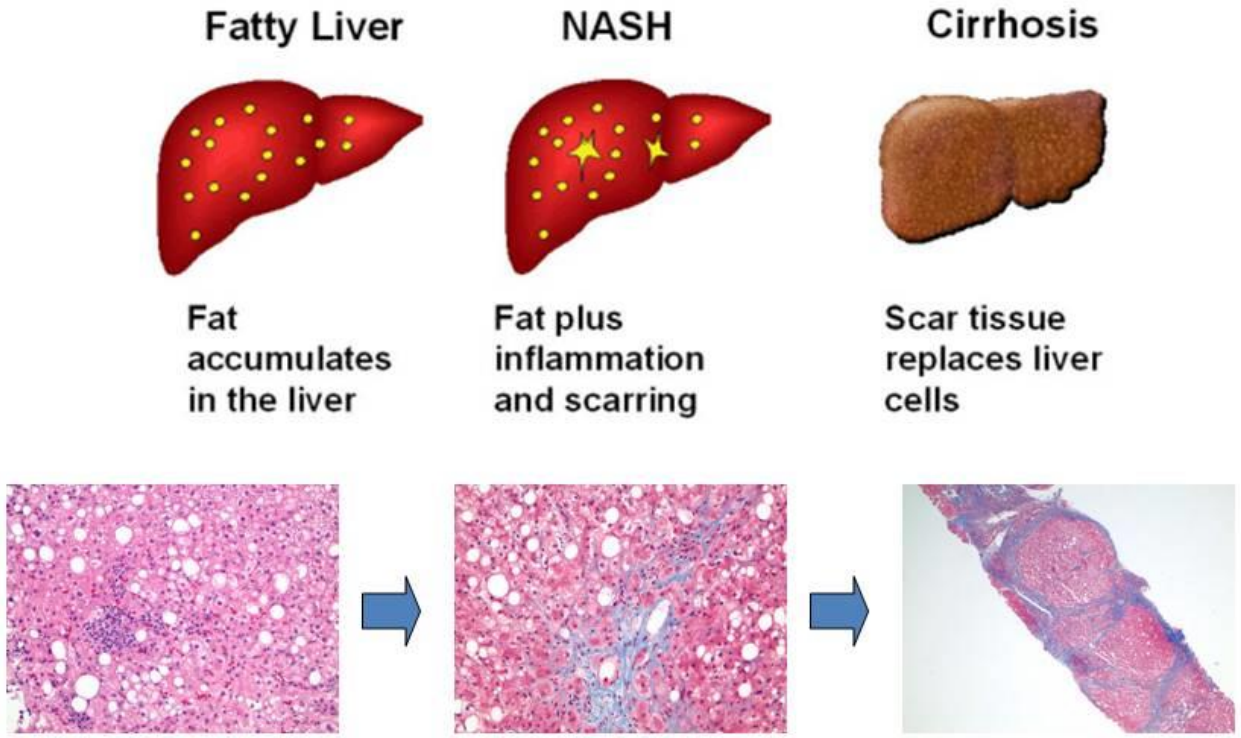
What is Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH)?



- Fat (triglyceride) accumulation in the liver in >5% of hepatocytes, in the absence of excessive alcohol consumption
- Inflammation, oxidative damage, scar tissue and eventually fibrosis
- Progressive disease
    - Can lead to cirrhosis, fibrosis and liver cancer
- Reversible until Cirrhosis

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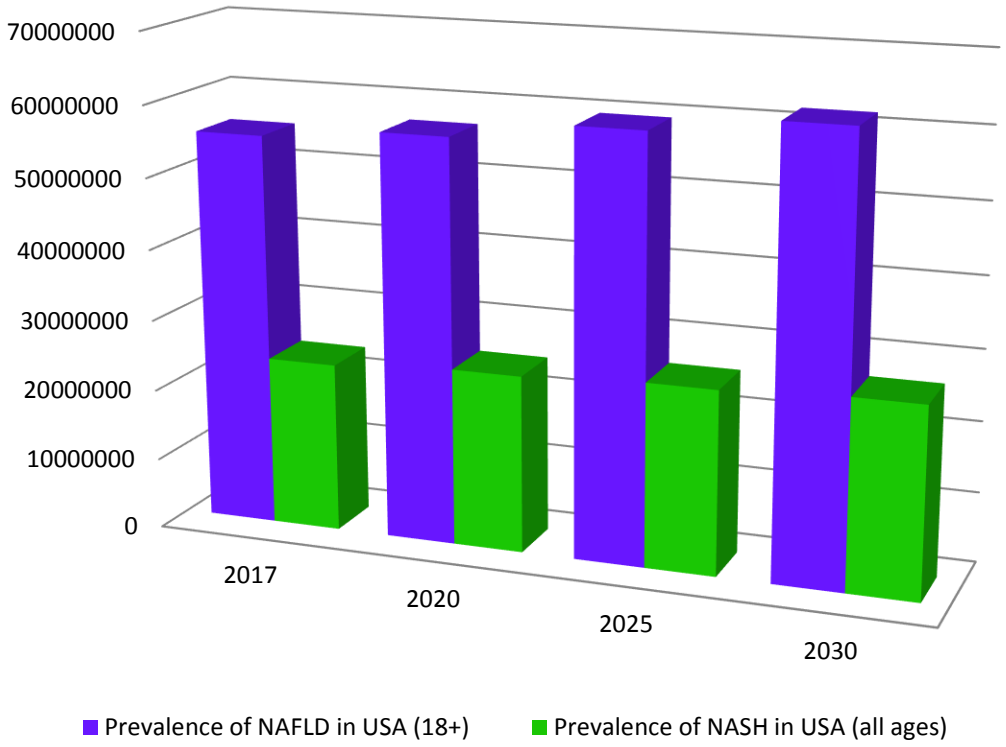
Sources: www.arthritis-rheumatism.com and Integrity Disease Briefings

What is the prevalence of NAFLD and NASH?



- Until recently considered to be relatively rare and harmless
- Growing global obesity epidemic
- NAFLD is the most prevalent chronic liver disease
- Projected to be the leading indication for liver transplant within the decade
- 2017 Prevalence
    - NAFLD – 24% North America, 25% Europe, 27% Asia, 30% South America
    - NASH – 7.5% USA, 5% UK, 5% Japan, 4% Worldwide

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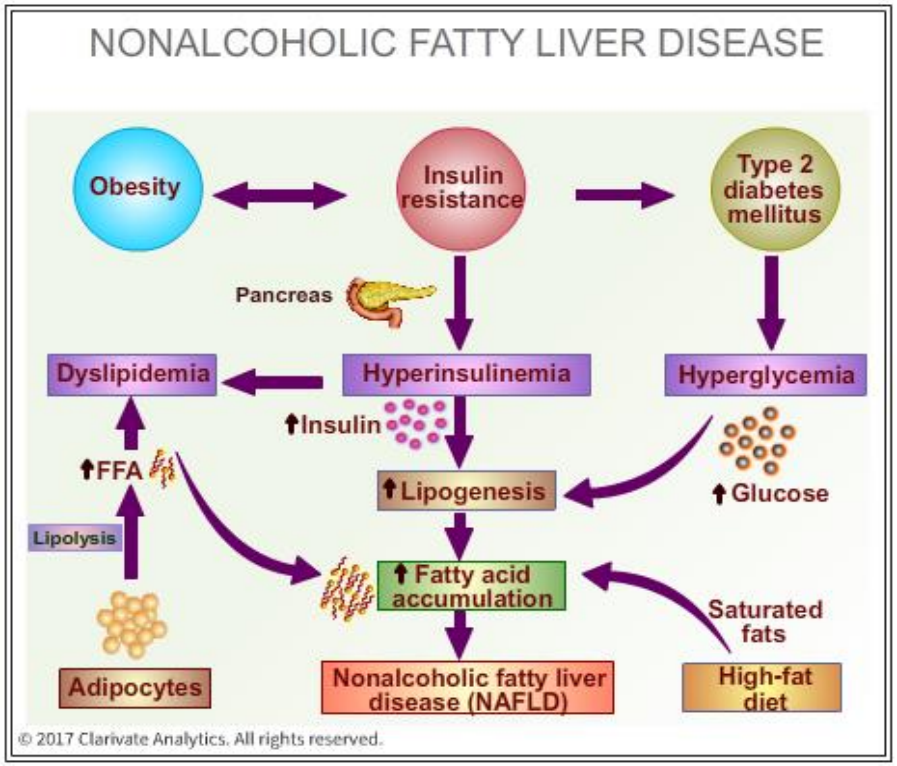
Sources: Clarivate IPD (Disease Forecasts) and Integrity Disease Briefings

What are the symptoms and risk factors for NAFLD and NASH?

Symptoms:
- Usually asymptomatic
- Abdominal discomfort
- Tiredness
- NASH:
    - jaundice
    - abdominal swelling
    - bleeding
    - fluid retention



Diagnosis:
- Liver function tests
- Liver enzyme tests
- Ultrasound or MRI
- Biopsy

Risk Factors:
- Obesity and old age
- Predisposing conditions - diabetes, hypertension and hyperlipidemia
- Ethnicity – e.g. Asian and Hispanic populations
- Lifestyle – high fat diets, smoking and inactivity
- Genetic factors – genetic polymorphisms
- Alterations in gut microbiome composition

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What are the potential treatments for NAFLD and NASH?

- First line: Intense lifestyle modifications

- Second line: Medical and surgical treatments BUT No approved drug for NASH
- Drugs being investigated for NAFLD and NASH

Drug Category	Representative	Mode of action
Anti-diabetics	Metformin, Pioglitazone	Improve insulin sensitivity
GLP1 analogues	Exenatide, Liraglutide	Suppress appetite, increase weight loss and increase insulin production
DPP4 inhibitors	Sitagliptin, Linagliptin	Enhances insulin production
Anti-oxidants	Vitamin E	Reduce oxidative stress
Statins	Atorvastatin	Lowers plasma lipids
Lipase inhibitors	Orlistat	Decrease fat absorption from intestine
Farnesoid XR agonist	Obeticholic acid	Reduce steatosis and inflammation
PPAR-α/γ agonist	Elafibranor	Reduce steatosis, inflammation and fibrosis

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Sources: Pappachan, J.M. *et al* J Clin and Trans Hepat (2017) 5: 384-393; Neuschwander-Tetri, B.A. BMC Medicine (2017) 15: 45-50; Clarivate IPD and Integrity Disease Briefings

How to discover novel druggable targets for NASH and NAFLD?

Problem:

- Complex genetic factors and Multi-factorial disease
- Lack of validated clinical trial endpoints
- Scattered information
- Difficulty in prioritizing druggable targets

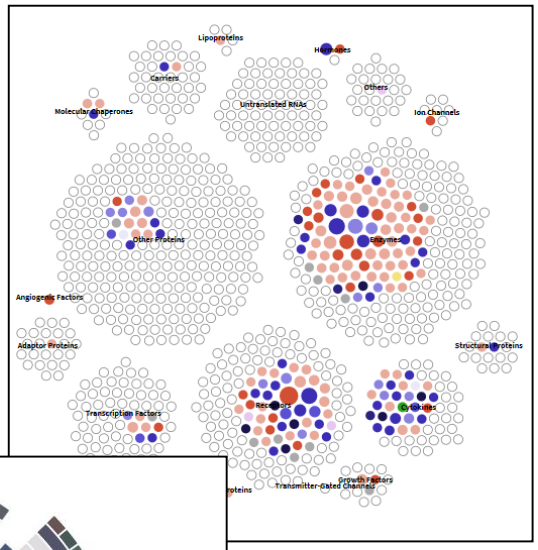
Solution:

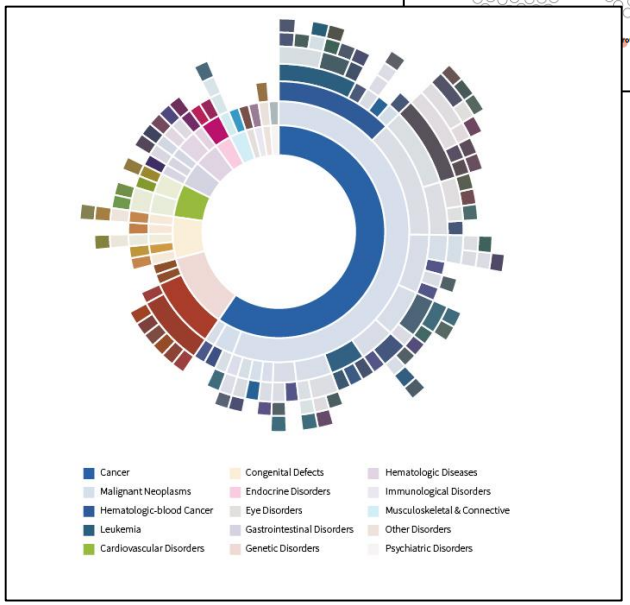
- Database of curated scientific data which rank targets based on evidence to support target/disease association
    - Identify novel targets in causative areas (metabolic, inflammation, fibrosis)
        - Consider a combination approach

Target Druggability

- Allows users to effectively visualize and analyze target/disease information
- Enhanced target information – Integrity and Metacore
- Simple, easy to use interface
- Customized Exploration views – group by target family, highest phase or genetic evidence
- Protein Atlas tissue expression information
- Animal models, References, Patents and Biomarker information

- **LIVE Demo** - Drug Research Advisor (DRA)





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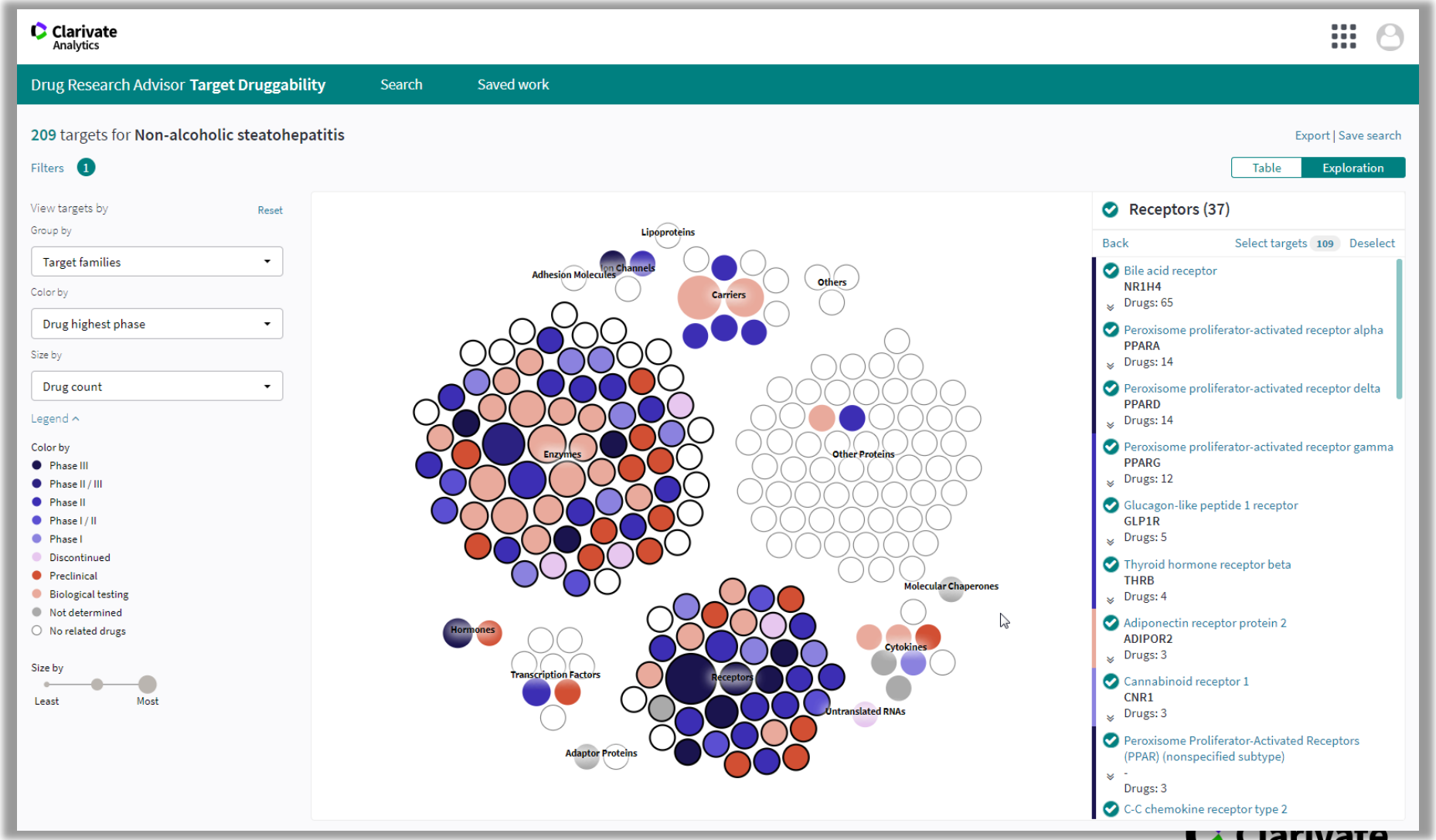
Novel targets for NASH

A search of *Drug Research Advisor* for NASH retrieves 209 Targets (109 enzymes + receptors).



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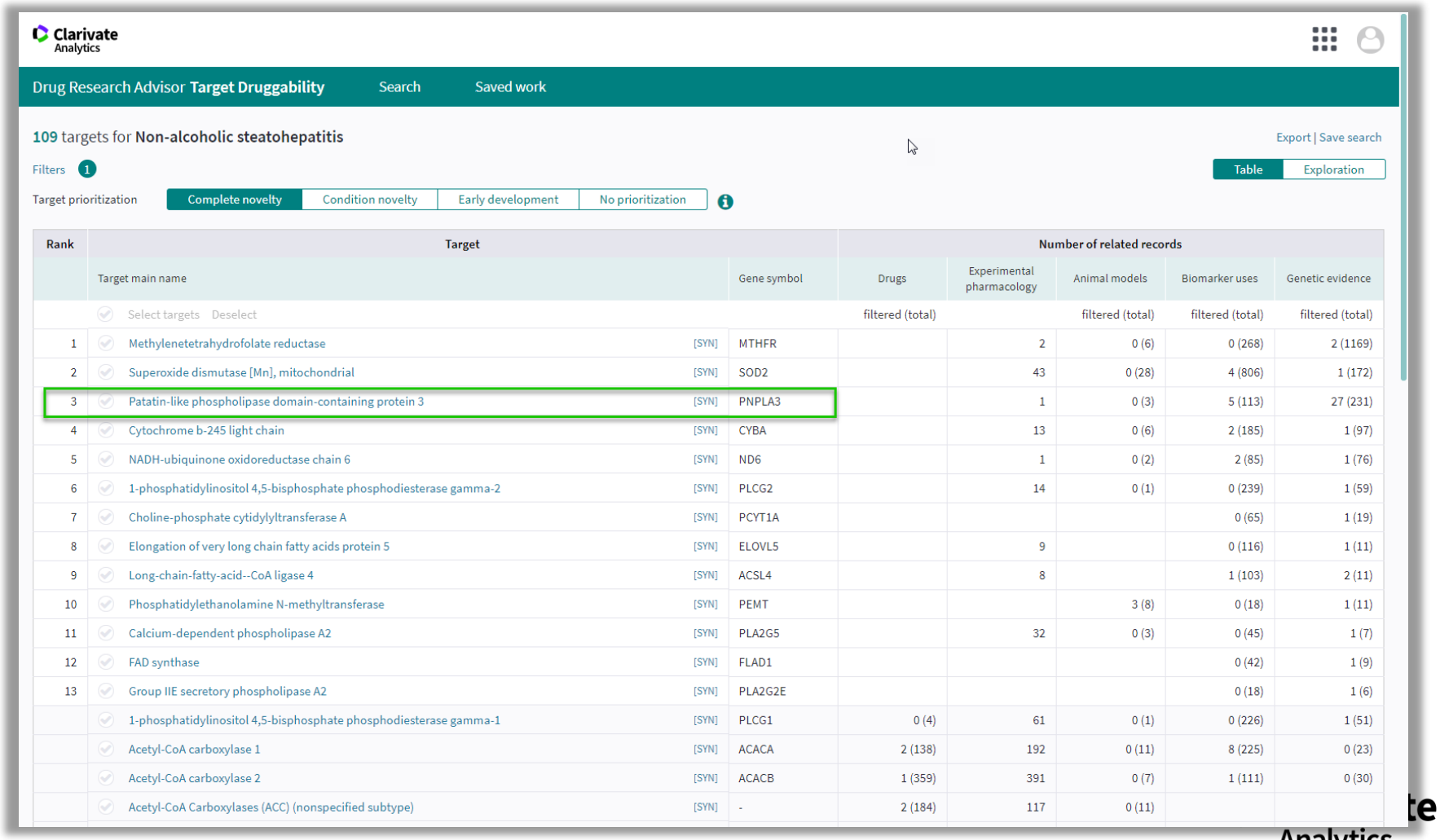
Narrowing the search for a novel target for NASH

If these 109 enzymes + receptors are prioritized by “Complete novelty,” **Patatin-like phospholipase domain-containing protein 3 (PNPLA3)** is ranked 3rd.



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Drug Research Advisor **Target Druggability** Search Saved work

109 targets for **Non-alcoholic steatohepatitis**

Export | Save search

Filters 1

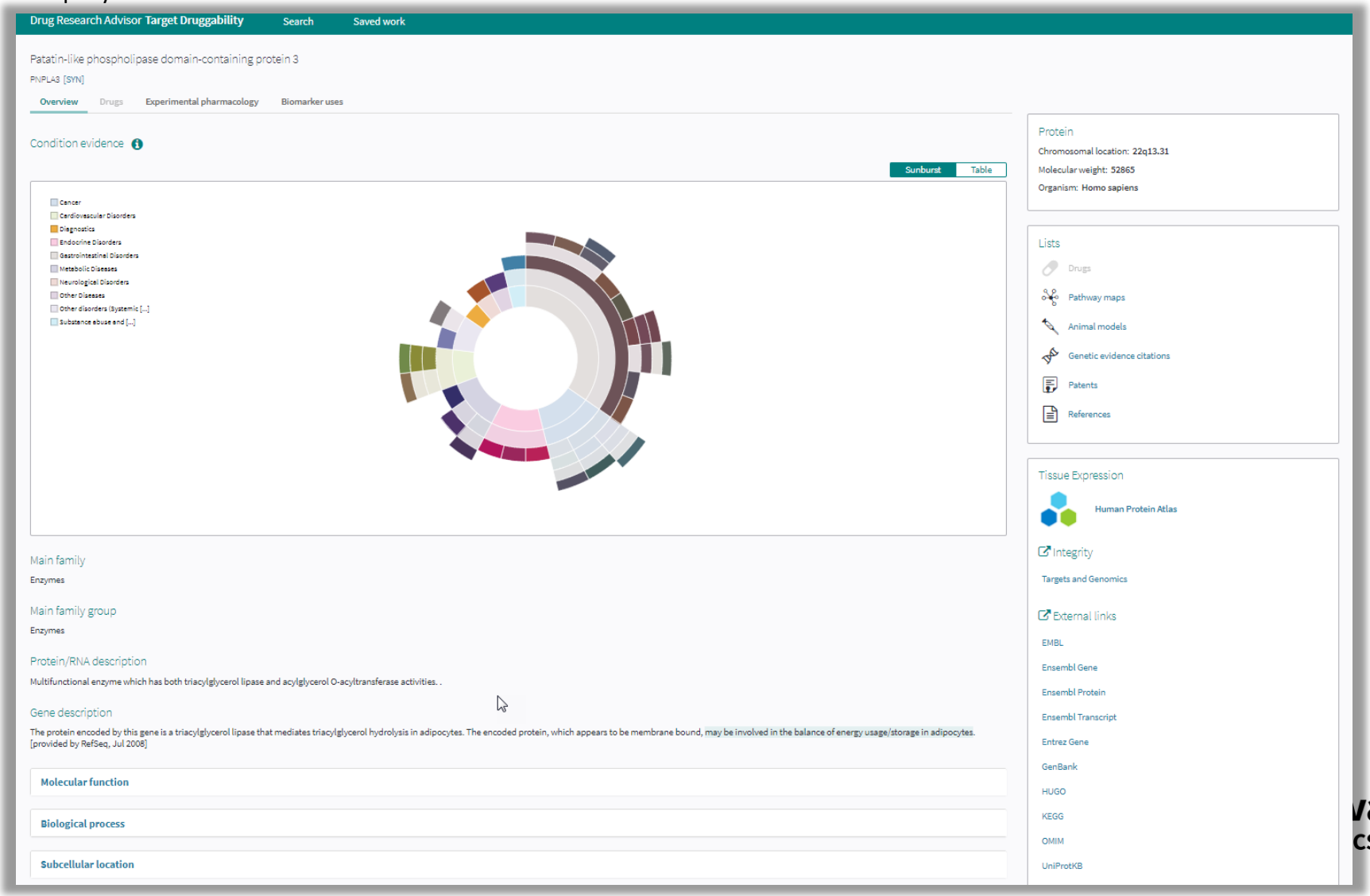
Table | Exploration

Target prioritization: Complete novelty | Condition novelty | Early development | No prioritization

Rank	Target		Number of related records				
	Target main name	Gene symbol	Drugs	Experimental pharmacology	Animal models	Biomarker uses	Genetic evidence
	Select targets Deselect		filtered (total)		filtered (total)	filtered (total)	filtered (total)
1	Methylenetetrahydrofolate reductase [SYN]	MTHFR		2	0 (6)	0 (268)	2 (1169)
2	Superoxide dismutase [Mn], mitochondrial [SYN]	SOD2		43	0 (28)	4 (806)	1 (172)
3	Patatin-like phospholipase domain-containing protein 3 [SYN]	PNPLA3		1	0 (3)	5 (113)	27 (231)
4	Cytochrome b-245 light chain [SYN]	CYBA		13	0 (6)	2 (185)	1 (97)
5	NADH-ubiquinone oxidoreductase chain 6 [SYN]	ND6		1	0 (2)	2 (85)	1 (76)
6	1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-2 [SYN]	PLCG2		14	0 (1)	0 (239)	1 (59)
7	Choline-phosphate cytidylyltransferase A [SYN]	PCYT1A				0 (65)	1 (19)
8	Elongation of very long chain fatty acids protein 5 [SYN]	ELOVL5		9		0 (116)	1 (11)
9	Long-chain-fatty-acid--CoA ligase 4 [SYN]	ACSL4		8		1 (103)	2 (11)
10	Phosphatidylethanolamine N-methyltransferase [SYN]	PEMT			3 (8)	0 (18)	1 (11)
11	Calcium-dependent phospholipase A2 [SYN]	PLA2G5		32	0 (3)	0 (45)	1 (7)
12	FAD synthase [SYN]	FLAD1				0 (42)	1 (9)
13	Group IIE secretory phospholipase A2 [SYN]	PLA2G2E				0 (18)	1 (6)
	1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-1 [SYN]	PLCG1	0 (4)	61	0 (1)	0 (226)	1 (51)
	Acetyl-CoA carboxylase 1 [SYN]	ACACA	2 (138)	192	0 (11)	8 (225)	0 (23)
	Acetyl-CoA carboxylase 2 [SYN]	ACACB	1 (359)	391	0 (7)	1 (111)	0 (30)
	Acetyl-CoA Carboxylases (ACC) (nonspecified subtype) [SYN]	-	2 (184)	117	0 (11)		

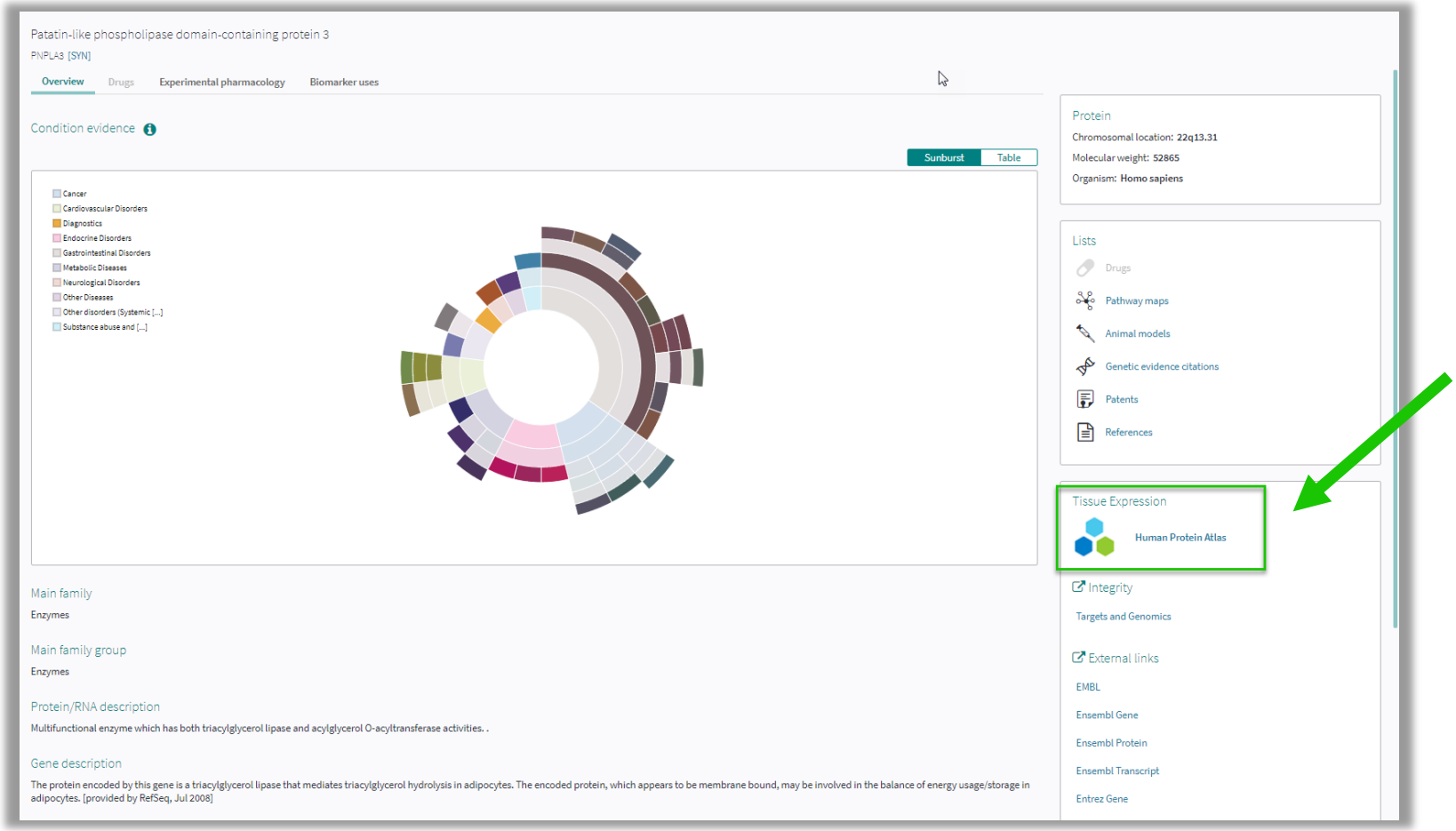
Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH

Patatin-like phospholipase domain-containing protein 3, also known as adiponutrin, is a membrane protein with triacylglycerol lipase activity that mediates triacylglycerol hydrolysis in adipocytes. It may be involved in the balance of energy usage/storage in adipocytes.



Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH

Tissue expression of Patatin-like phospholipase domain-containing protein 3 can be viewed from the Link tor The Human Protein Atlas.



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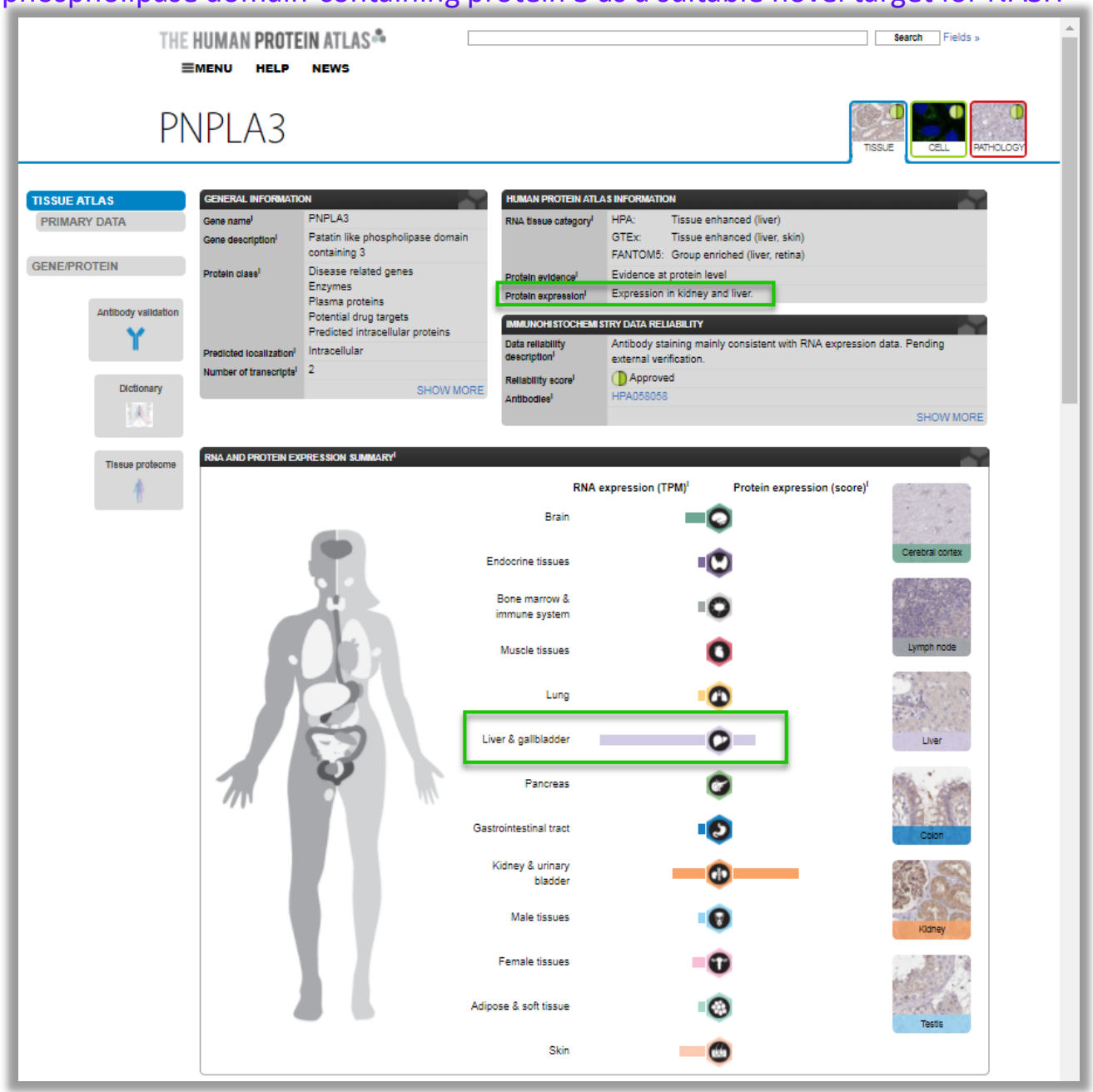
Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH



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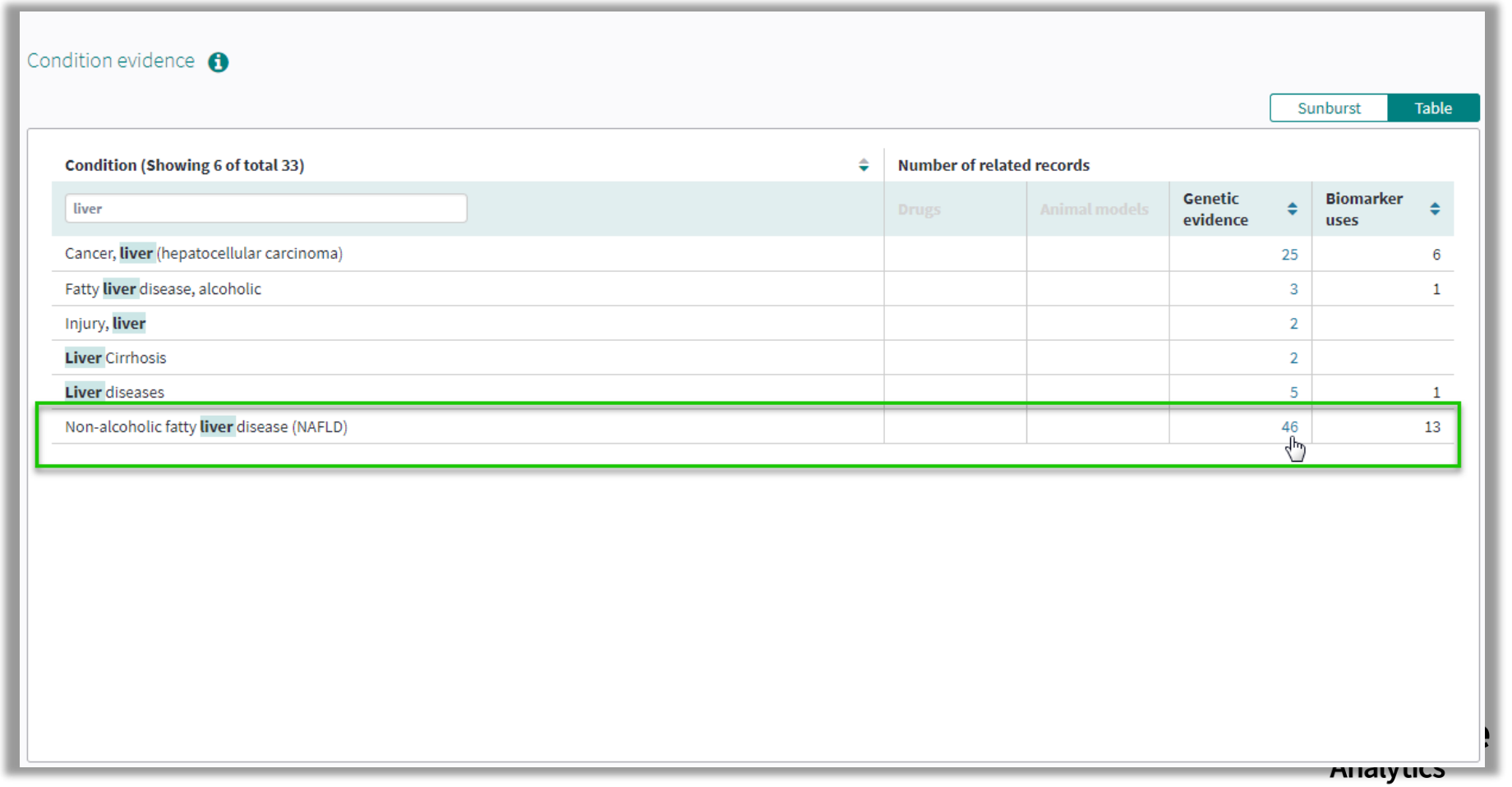
Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH

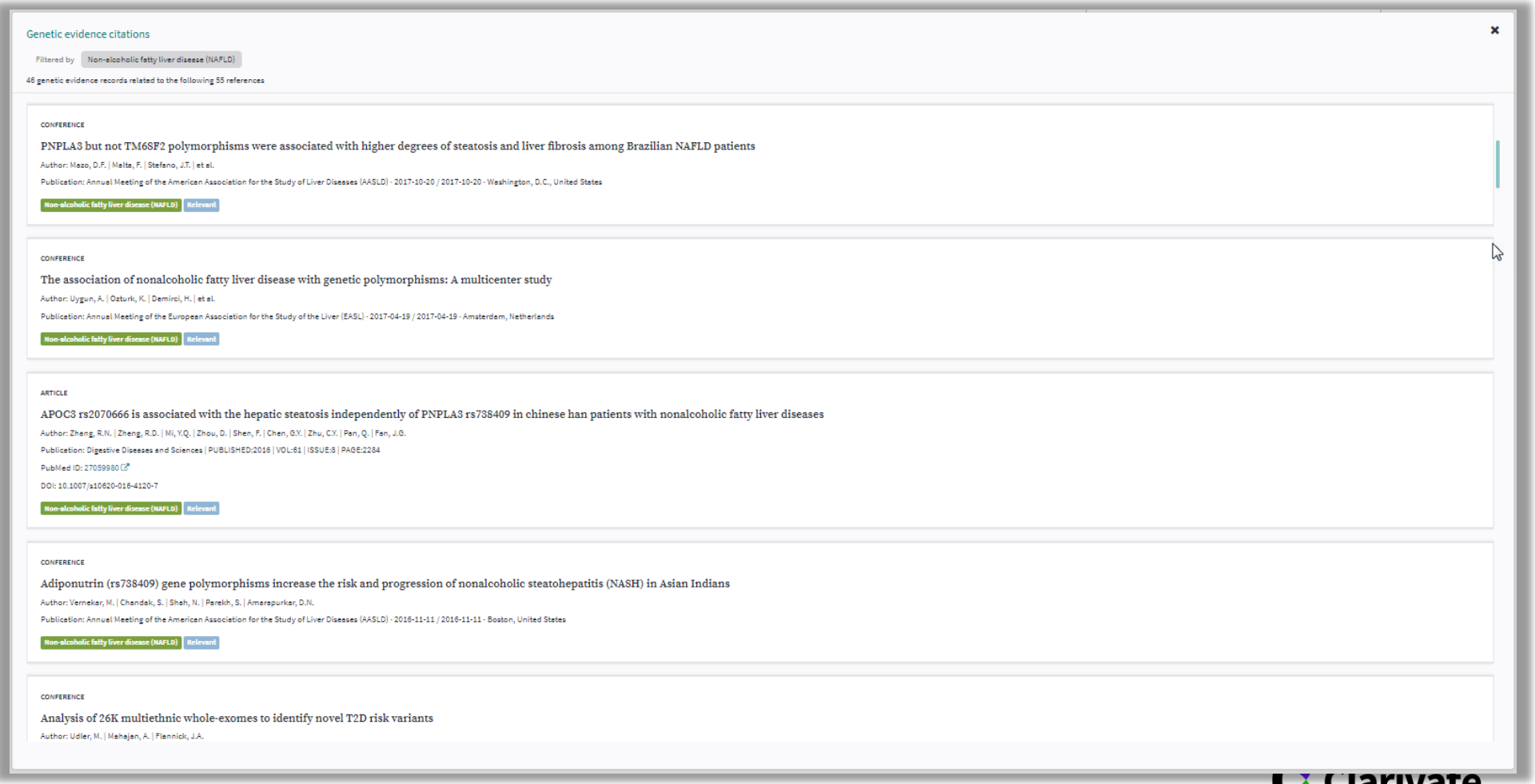
Genetic Evidence

Genetic evidence for Patatin-like phospholipase domain-containing protein 3 as a target in NASH can be viewed from the 55 literature, conference and patent citations which have identified specific genetic polymorphisms in Genetic evidence for Patatin-like phospholipase domain-containing protein 3 that are associated with a greater risk of NASH.



Genetic evidence for Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH
References

Examination of references suggests that Genetic evidence for Patatin-like phospholipase domain-containing protein 3 could be a valid target for the treatment of NASH.



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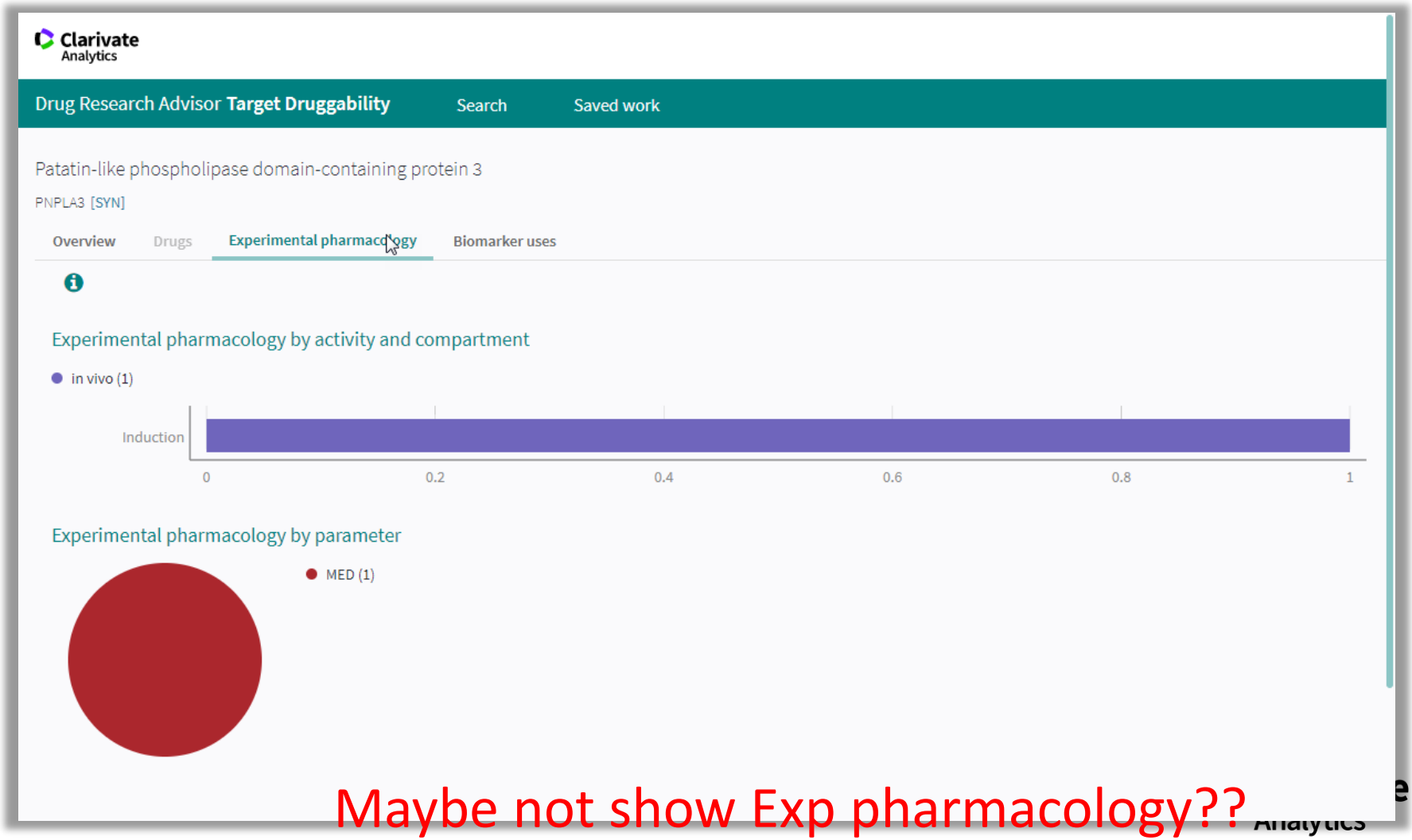
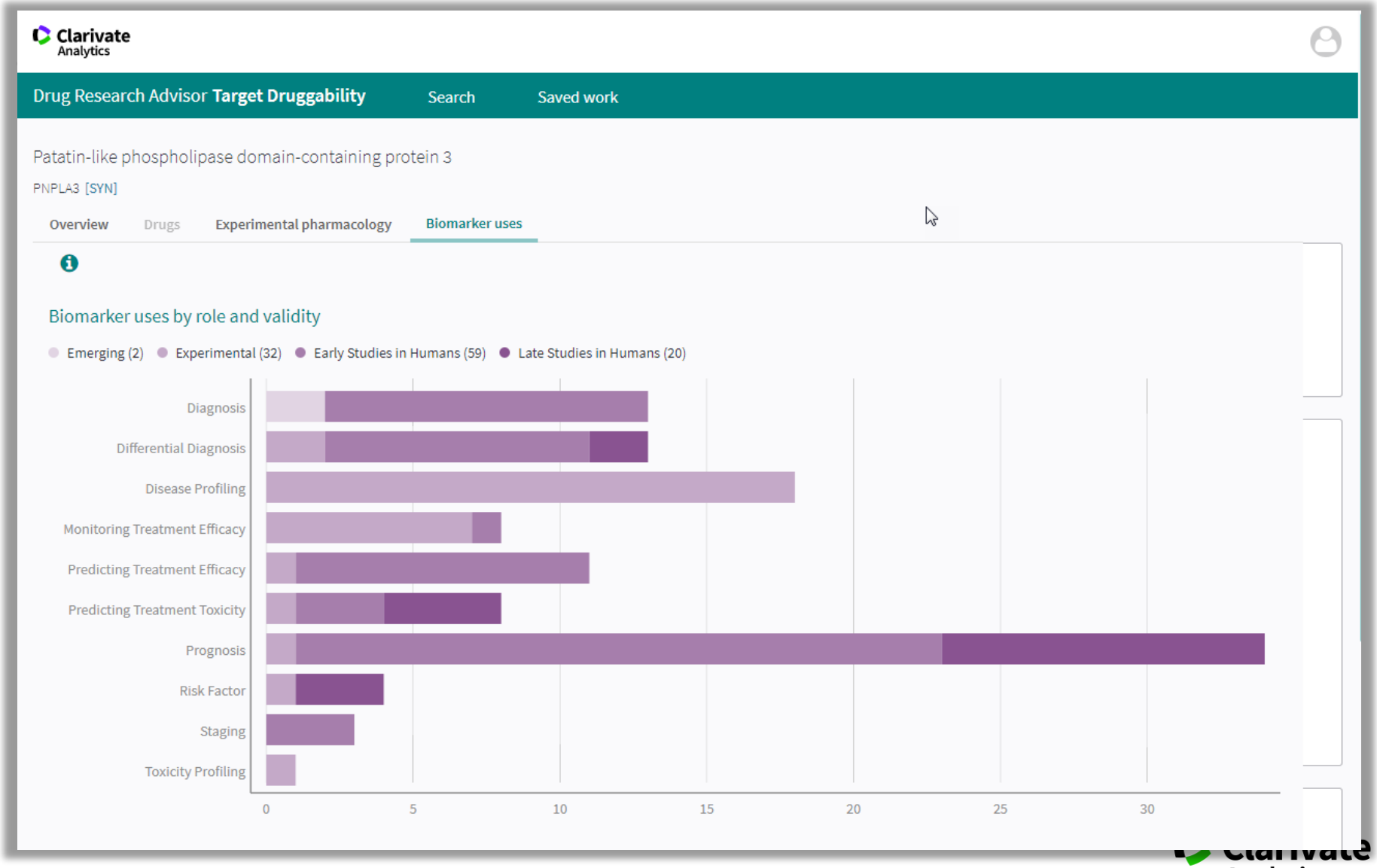
Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH
Experimental Pharmacology

Examination of Experimental Pharmacology data associated with Patatin-like phospholipase domain-containing protein 3 and NASH suggests that Patatin-like phospholipase domain-containing protein 3 could be a valid target for the treatment of NASH.



Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH
Biomarkers



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