

Shifting the needle on the burden of MASLD and metabolic health

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Disclosures

[Arun J. Sanyal]

I disclose the following financial relationship(s) with a commercial interest:

- Ownership interests: Durect, Tiziana, Genfit, Exhalenz, Northsea, Rivus, Inversago
- Consultant: Gilead, Intercept, Novartis, Novo Nordisk, Inventiva, Merck, Pfizer, Boehringer Ingelhiem, Bristol Myers Squibb, Eli Lilly, Genentech, Amgen, Alnylam, Regeneron, Thera Technologies, Madrigal, Salix, Malinckrodt, Gatehouse, Rivus, Siemens, Lipocine, 89 Bio, Astra Zeneca, Akeru, Foresite, Mitopower, Histoindex, Path AI, Takeda
- Grant support to school: Gilead, Intercept, Novartis, Novo Nordisk, Inventiva, Eli Lilly, Genentech, Boehringer Ingelhiem, Bristol Myers Squibb

Love the outdoor

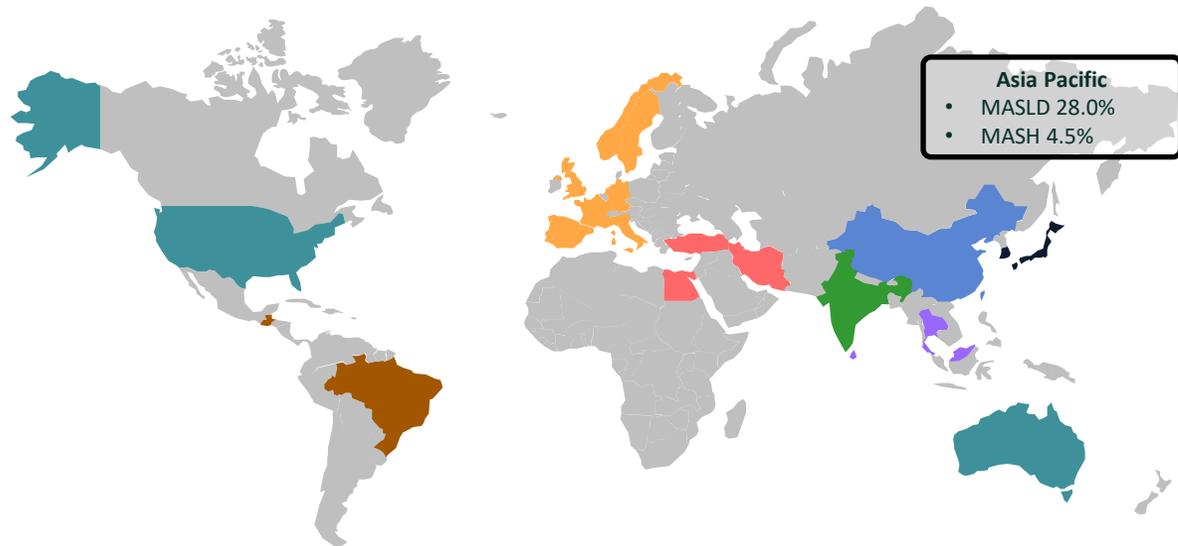


With my family

The global burden of MASLD is increasing and linked to the pandemic of obesity

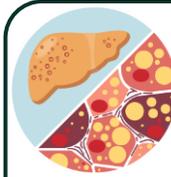


Global prevalence* of MASLD is 30.1% and MASH is 5.3%¹

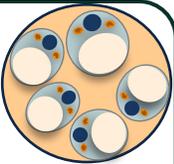


Regional prevalence shows some variation

- MASLD ranges from 25.1% (Western Europe) to 44.4% (Latin America)
- MASH ranges from 4.0% (Western Europe) to 7.1% (Latin America)



Global prevalence of MASLD and MASH in people living with overweight/obesity²



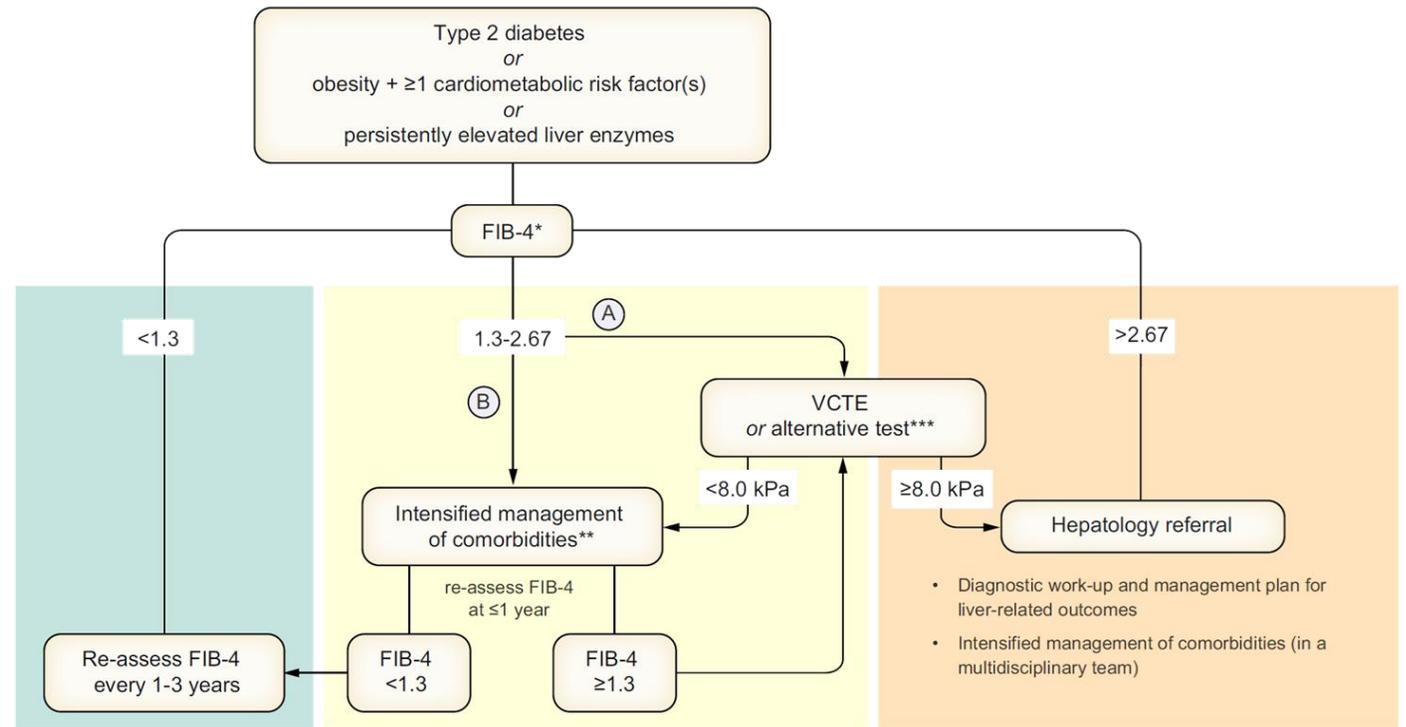
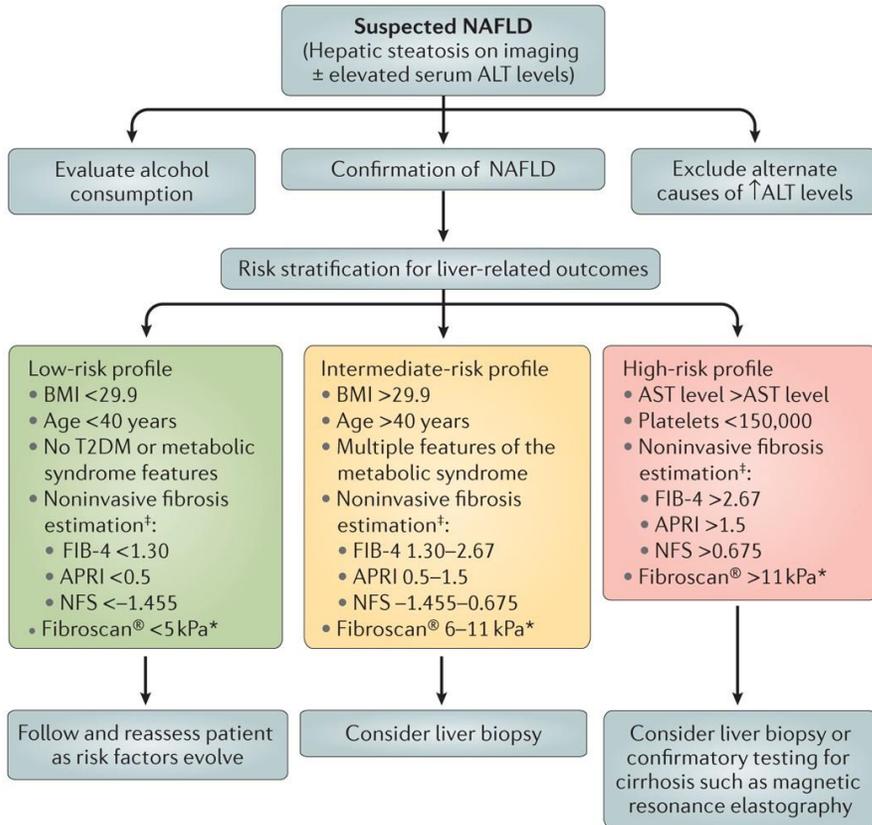
- Systematic review and meta-analysis
- N=101 028

	Overweight	Obesity
Prevalence of MASLD (%)	70.0	75.3
Prevalence of MASH (%)	33.5	33.7

*MASLD prevalence in general population (>20 years) from 1990 to 2019. MASH prevalence was calculated by multiplying the prevalence of MASH in MASLD patients with the prevalence of MASLD in the general population. MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; T2D, type 2 diabetes. 1. Younossi et al. Hepatology 2023;77:133; 2. Quek et al. Lancet Gastroenterol Hepatol 2023;8:20.

NASH/MASH- A 10 year report card!

Only incremental changes in approaches to identify cases

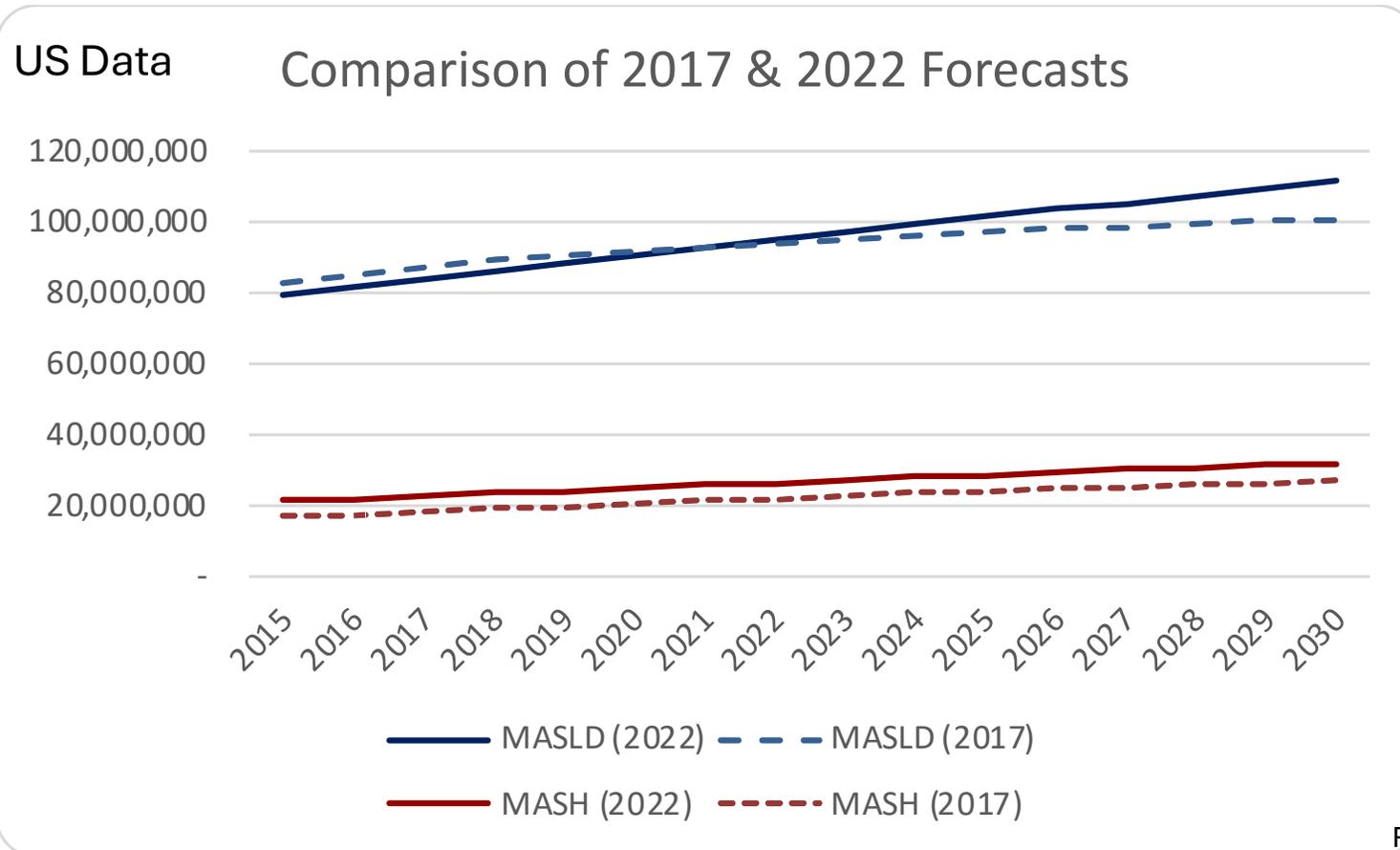


Nature Reviews | Gastroenterology & Hepatology

While Resmetirom is now approved conditionally, it is expensive and there is no access to drug globally
While many drugs are in development, they are also likely to be expensive and will face similar issues related to access

In the meantime, the burden of MASLD and MASH continue to rise!

Global trends for MASLD and MASH continue to rise as well



Razawi et al, AASLD 2023



LOOKING AT THE PROBLEM THROUGH DIFFERENT VIEWPOINTS

An analysis of why progress has been slow

HCV-a case study

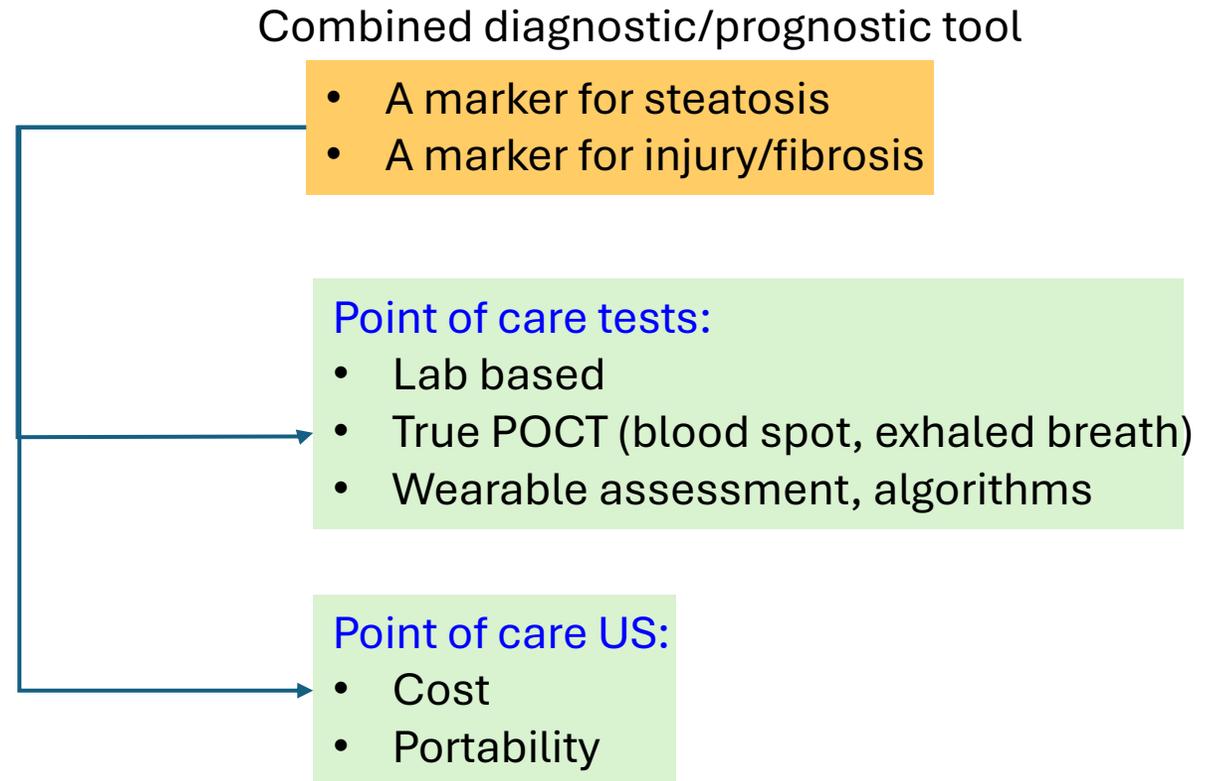
- No issues with nomenclature
- Case definition unambiguous
- Major advances in point of care testing
- Clear guidelines present
- Value proposition well established
- Not confounded by comorbidity profiles and their role in the liver disease

Barriers for progress in MASH

- Nomenclature still debated by some
- Case definitions based on histology which is not used by 90%+ of practicing providers worldwide
- Lack of tools to identify patients everywhere
- Unclear when to start screening, how often to repeat
- Value proposition of early detection not established
- Common perception that treating obesity and diabetes will fix the problem

Establishing research priorities- focus on point of care testing without breaking the bank!

- Nomenclature is still debated!
- ***Do we have tools we can afford that can be used everywhere?***
- ***Screen for fat or fibrosis?***
- Diagnostic criteria unclear for primary care implementation?
- Is it curable?
- What age to start screening?
- Managing cost



Establish repeatability, reproducibility, analytic robustness upfront.

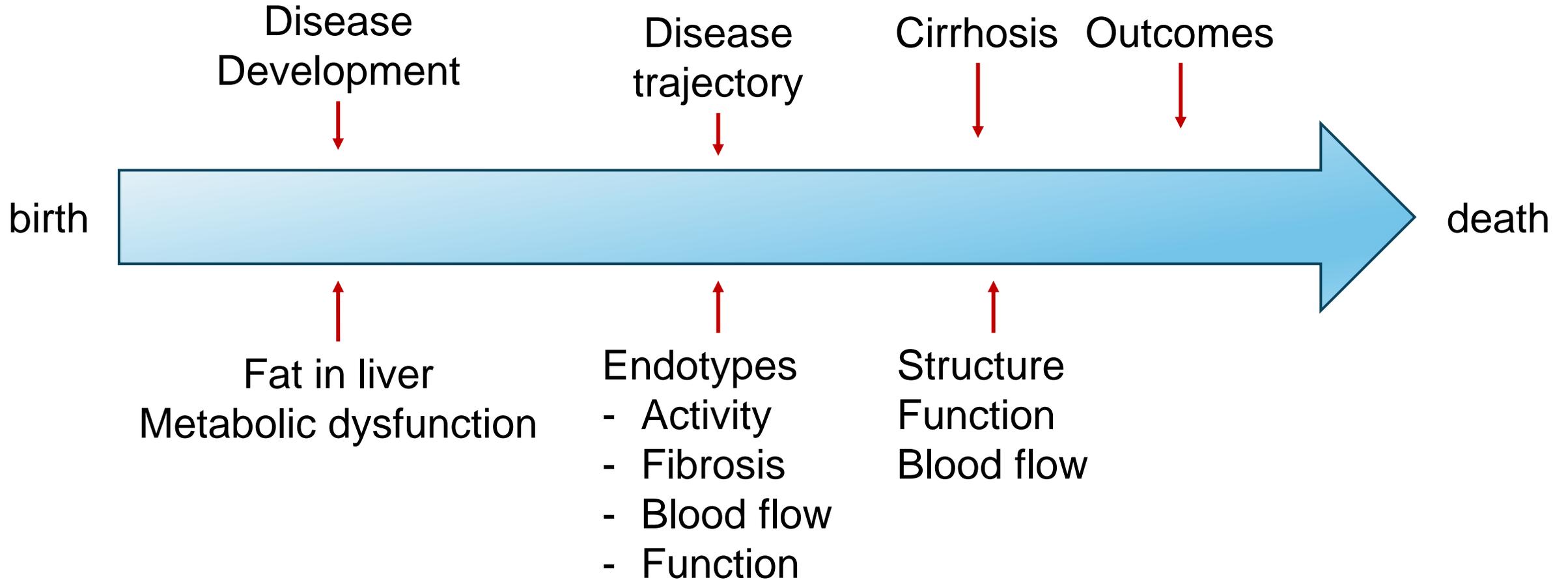


Establishing research priorities- case definitions should be fit for purpose, widely deployable and lead to actionable care pathways

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- ***Diagnostic criteria unclear for primary care implementation?***
- Is it curable/containable?
- What age to start screening?
- Care at what cost?-

- **MUST BE BASED ON:**
 - Clinical criteria
 - Simple NIT criteria
 - NITs that can be implemented at scale globally
 - COST is an important consideration!!

Case definitions must be actionable in the field globally



Making the case for FIB-4 for a key public health strategy for global purposes

- CBC/platelets + Hepatic panel
- Widely available
- Surrogate for fibrosis a key prognostic marker
- Associated with prognosis
- Change in FIB-4 further linked to prognosis
- Linked to outcomes in general population and in known diseased populations

	Included Using FIB4 and/or LSM Criteria		
Rate per 100 Person years	Class A (n=554) <i>Fib4<1.3</i>	Class B (n=536) <i>Fib4 1.31-2.6</i>	Class C (n=846) <i>Fib4 > 2.6</i>
Deaths *	0.07	0.42	3.08
Liver events *	0.21	1.32	9.33
MACE *	0.83	1.60	2.54
HCC *	0	0.07	1.08

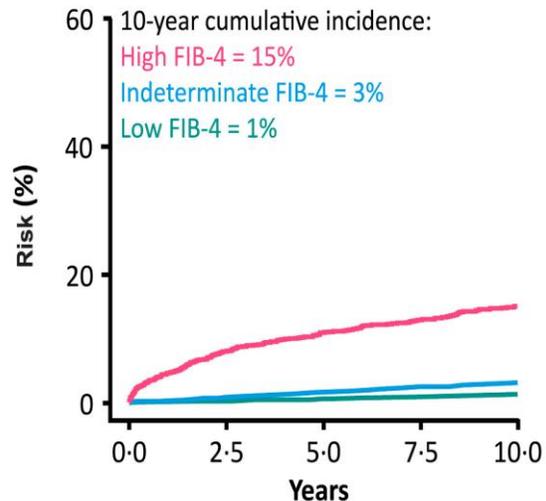
Sanyal et al, CGH 2023



FIB-4 predicts key clinical outcomes in obese populations and/or type 2 diabetes

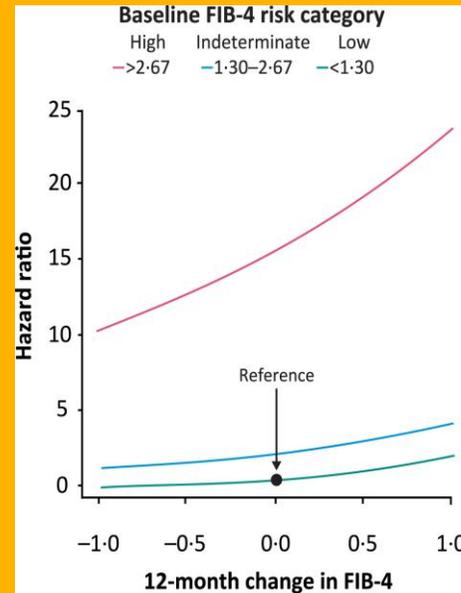
Liver events

A



Number at risk	0.0	2.5	5.0	7.5	10.0
High FIB-4	1864	1289	994	730	207
Indeterminate FIB-4	13,129	11,610	10,001	8095	2710
Low FIB-4	29,285	27,816	25,928	22,537	8281

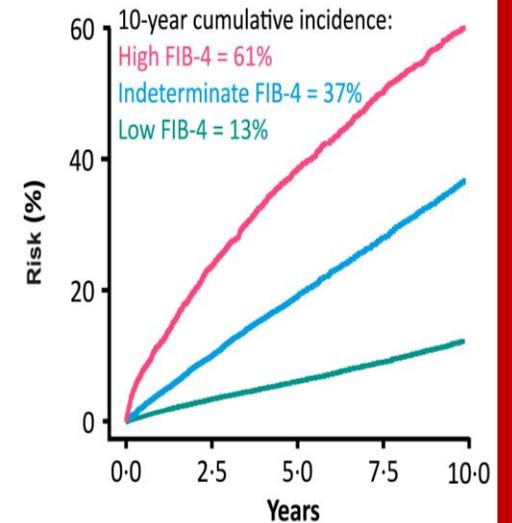
Changes over time



Baseline FIB-4 category	HR (95% CI)	
	1-unit FIB-4 increase	1-unit FIB-4 decrease
High FIB-4	24.27 (16.98-34.68)	10.90 (7.90-15.05)
Indeterminate FIB-4	4.48 (3.36-5.98)	1.67 (1.22-2.29)
Low FIB-4	2.48 (2.04-3.02)	0.40 (0.33-0.49)

mortality

C



Number at risk	0.0	2.5	5.0	7.5	10.0
High FIB-4	1931	1440	1091	799	223
Indeterminate FIB-4	13,180	11,710	10,119	8224	2761
Low FIB-4	29,333	27,892	26,027	22,650	8343

Total study population (n= 44,481)

Anstee et al, Lancet Regional Health-Europe, Vol 36, Jan 2024

It is time to rethink therapeutic approaches and public facing messaging!

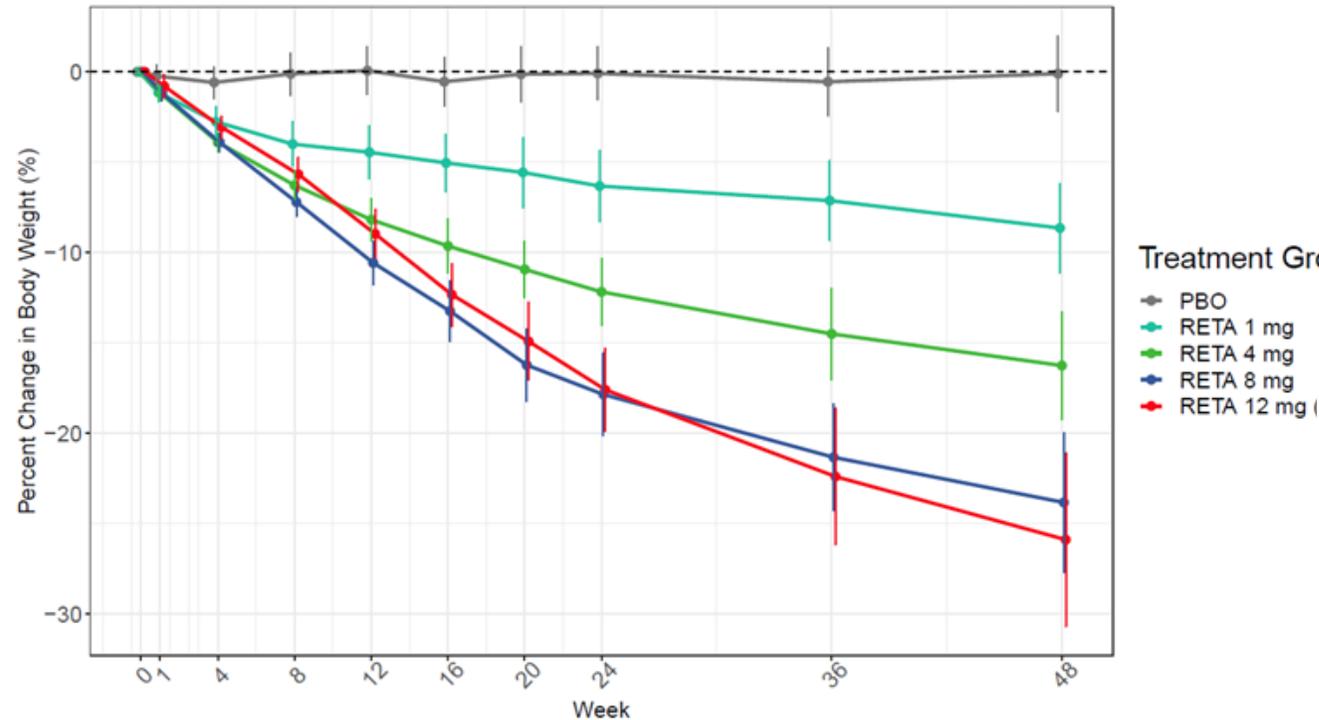
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- Care at what cost?- what has to be given up to make room for these costs?

- Excellent therapeutics are here and more are on their way
- COST is an important consideration!!

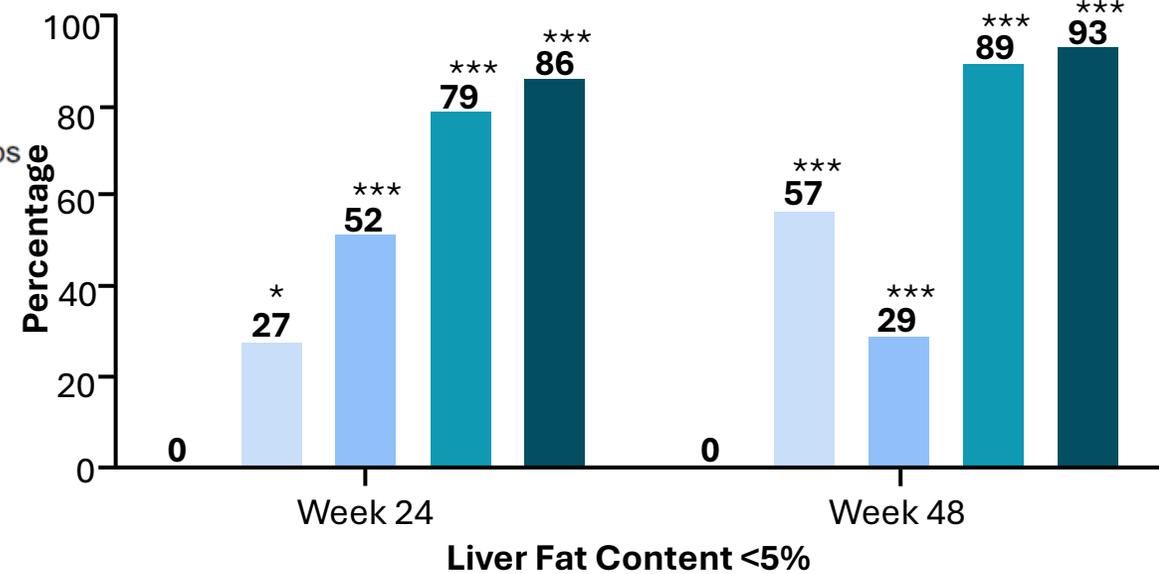


New therapeutics bring promise of massive weight loss and even wiping out MASLD without significant fibrosis

Percent Change in Body Weight (GZBF NAFLD Addendum)

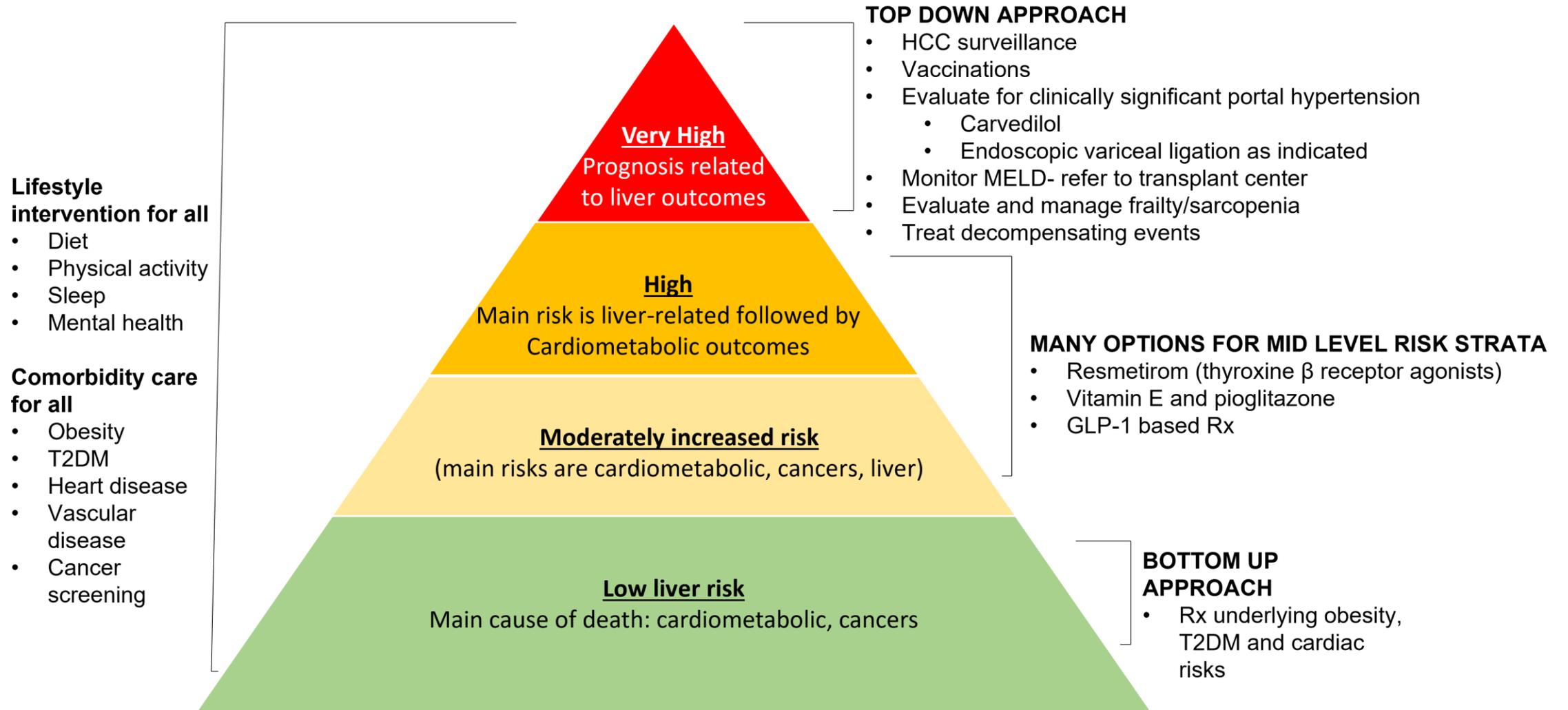


Jastreboff et al, N Engl J Med 2023; 389:514-526



Sanyal et al, Nature Medicine, June 2024

Therapeutics must focus on prevention of serious disease and not just on treatment of serious disease



Shah and Sanyal, in press, 2024

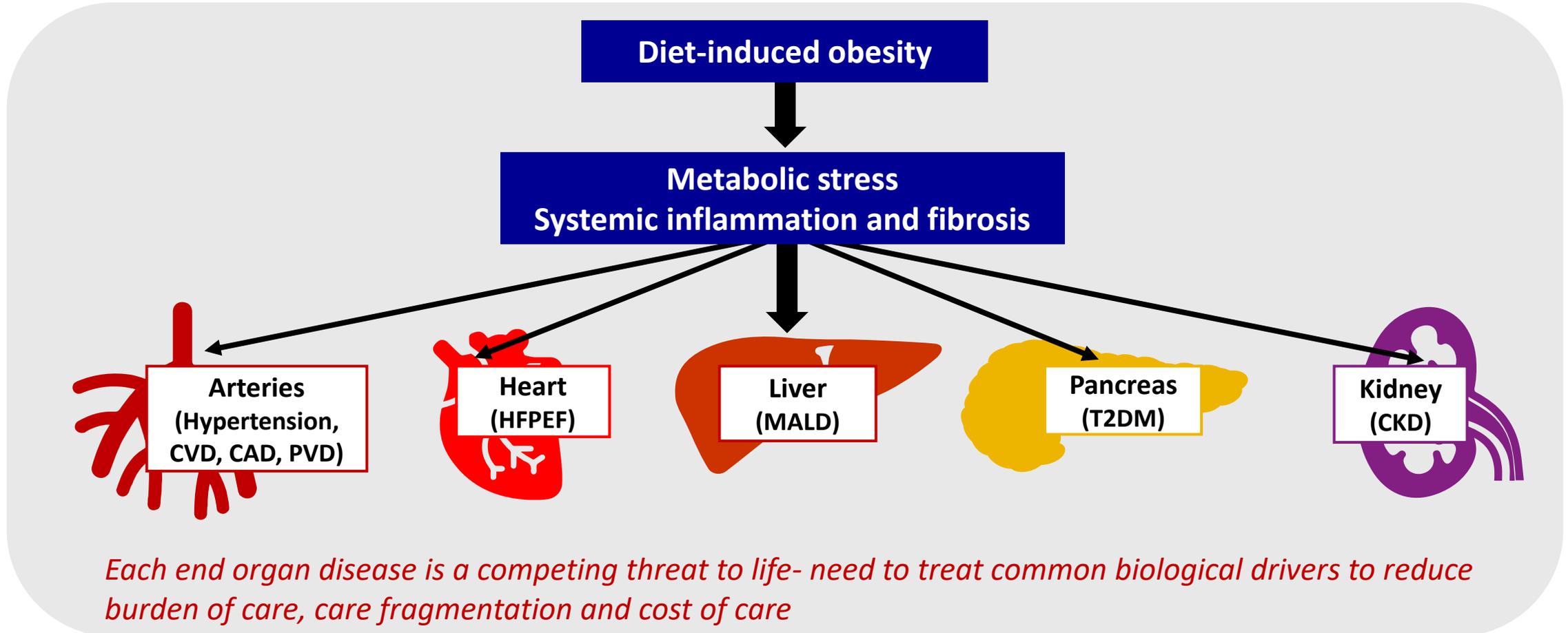
Establishing the value proposition of therapy has to be rethought!

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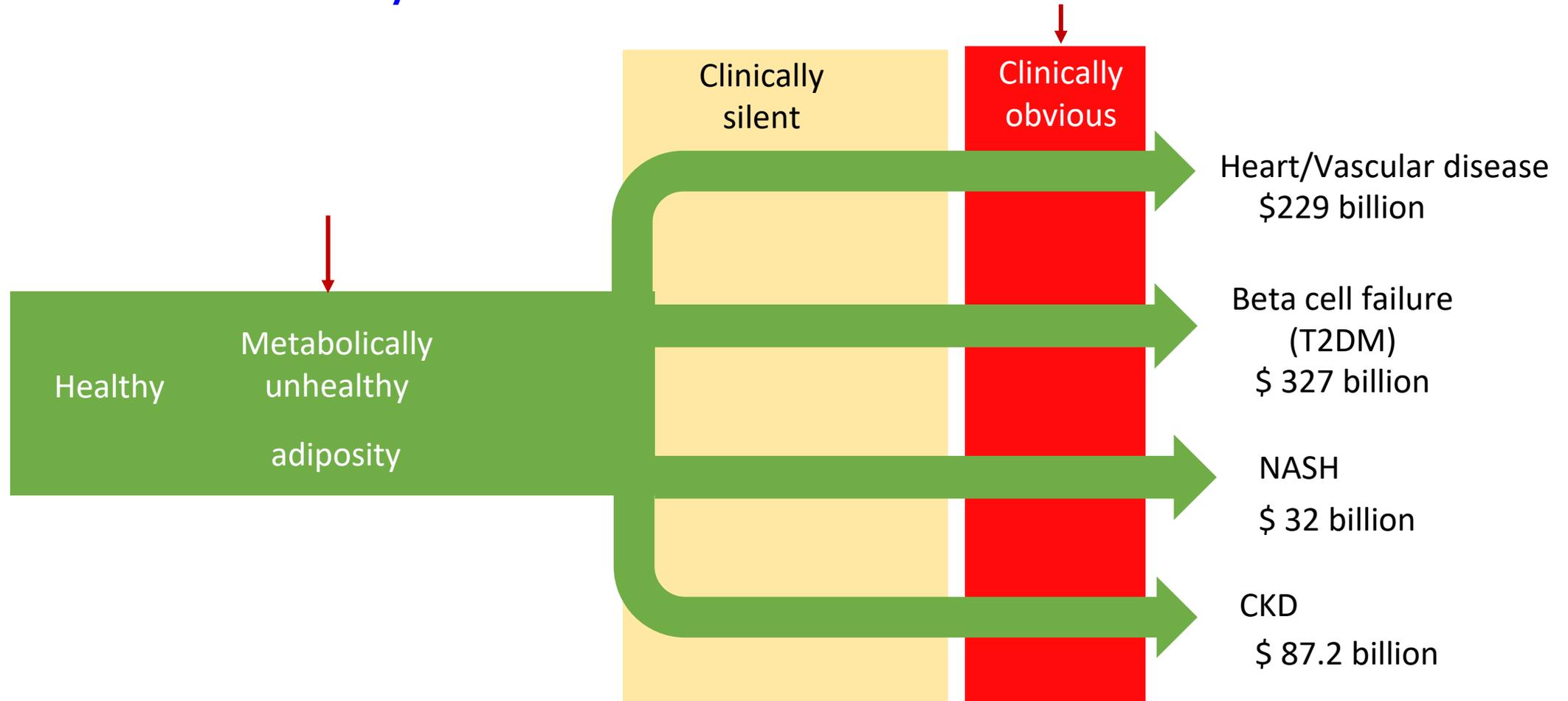
Focus on Prevention and Reversal of early disease
Focus on multi-organ targeted therapeutics



Value proposition of therapeutics- moving from MASLD to metabolic medicine- need well done medical economic models and to test economic hypotheses in real world trial settings



Current medical training and practice largely focuses on diagnosis and treatment of clinically obvious disease



Cost data from CDC

Takeaways- a global view

Staying alive- the greatest human safety concern



- **Accept** metabolic health related disorders as a human safety threat AND MASLD as an integral part of metabolic dysfunction
- **Develop** simple, robust clinical-NIT based case definitions that lend themselves for broad clinical-epidemiological application- don't make perfect the enemy of the good!
- **Challenge** Biotech/Device manufacturers to develop point of care tests
- **Leverage common biology** across key metabolic disease related organ disease for integrated therapeutic approaches
- **Model cost benefits-** from care integration, treating early

Thank you for your attention