Transitioning from pre to post – accelerated approval

Liver Forum 9

July 10th 2019, Paris, France

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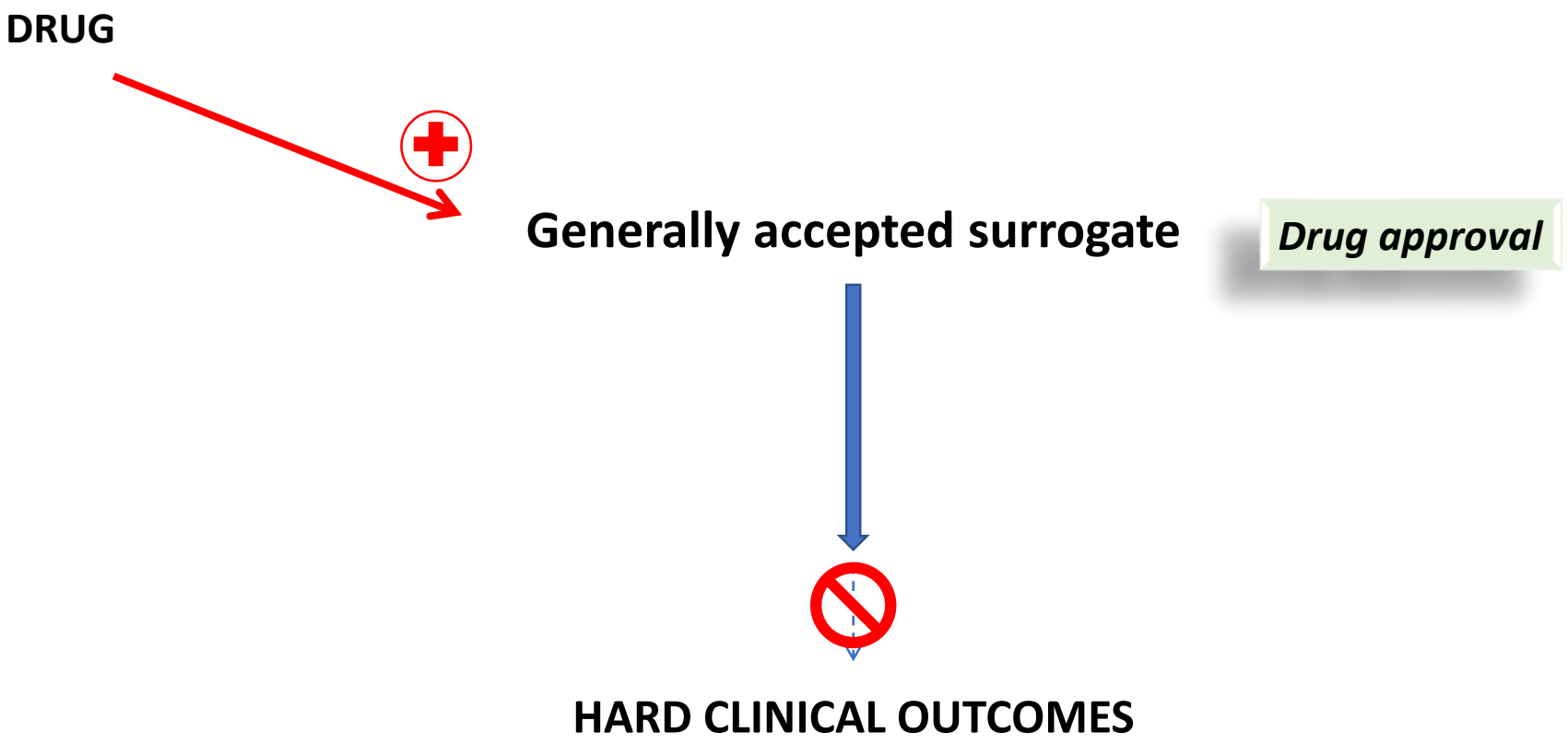
ICAN Institute of Cardiometabolism And Nutrition

faculté de médecine Pierre et Marie CURIE

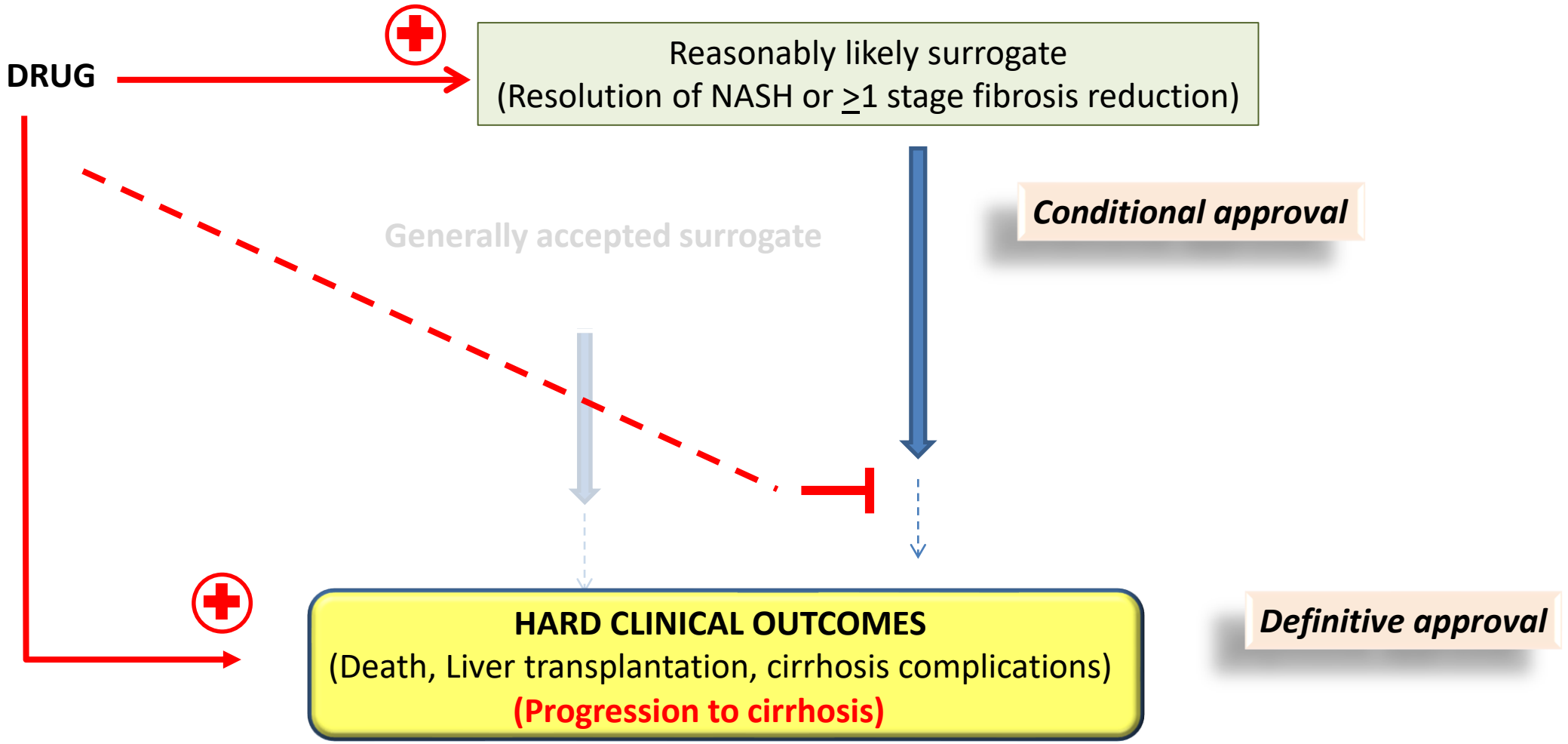
How will conditional approval change the current landscape?

- For trials
  - ➡ The demonstration of the predictive value of the likely surrogate
  - The need to continue the outcome trials
- For clinical practice

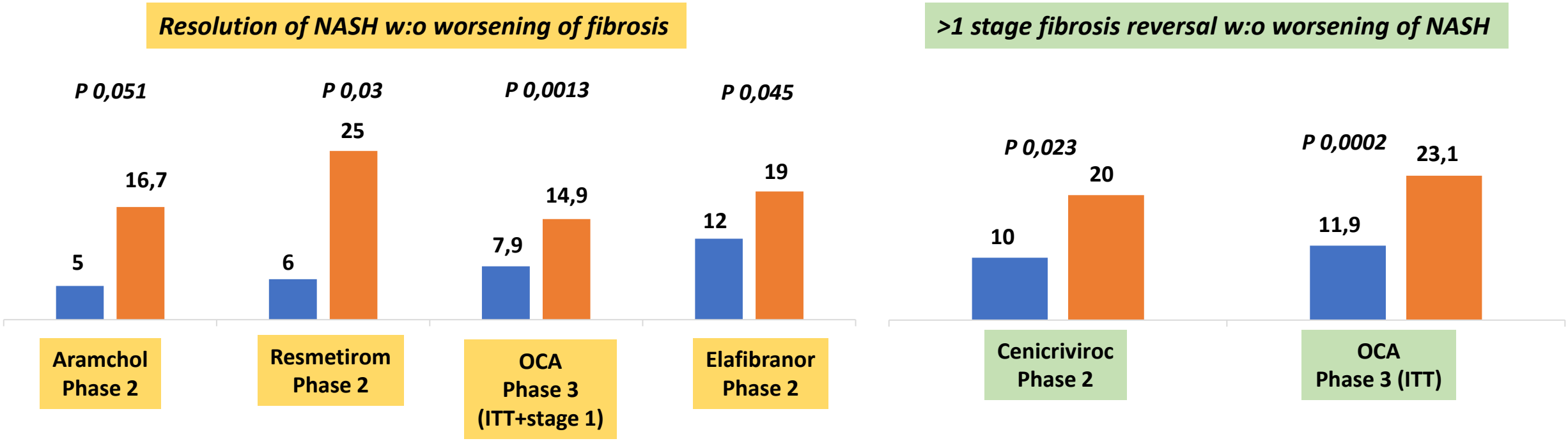
Validated surrogates for clinical outcomes – Shorter studies

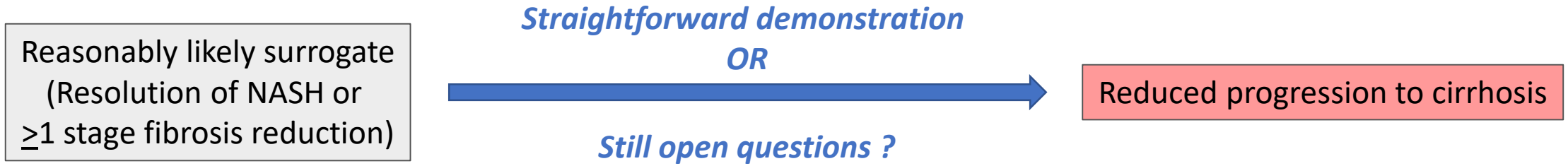


Accelerated pathway for approval (Registrational trials)



Performance (so far) on likely surrogates of drugs in development

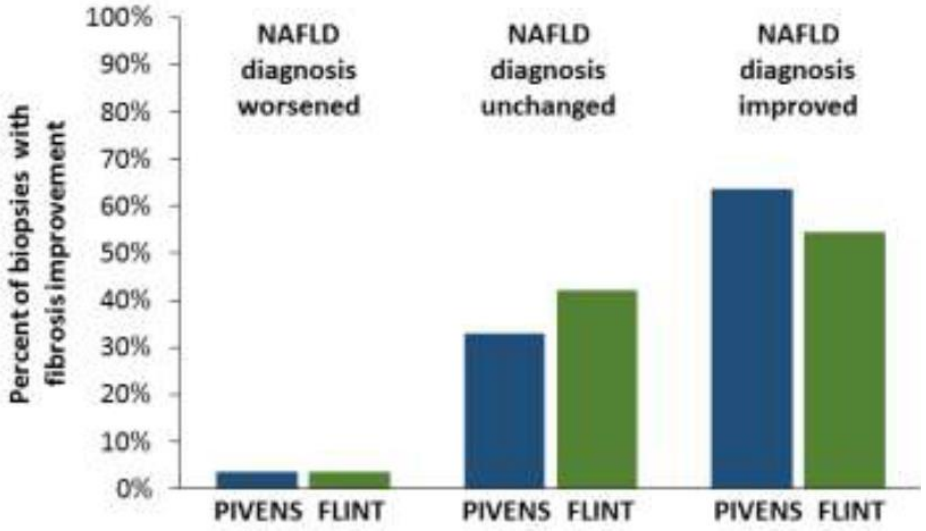


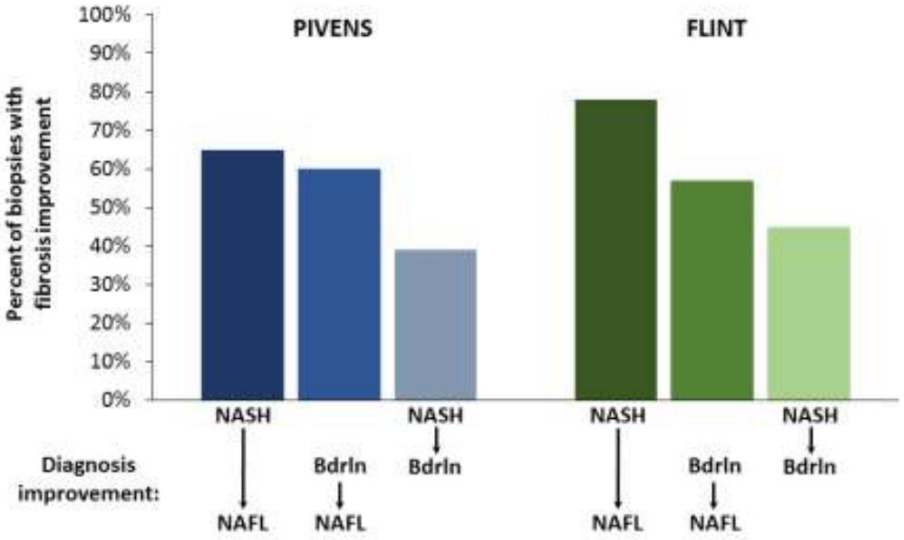


- Does improvement in disease activity predict less progression to cirrhosis to the same extent as NASH resolution ?

Fibrosis regression vs. changes in other histological features

Intergated database PIVENS (38% regression of fibrosis) and PIVENS (28%)





Histological features associated with fibrosis improvement :

- **NASH resolution +++**
- **NAS reduction**
- **Ballooning**
- **Mallory bodies**
- **Portal inflammation**

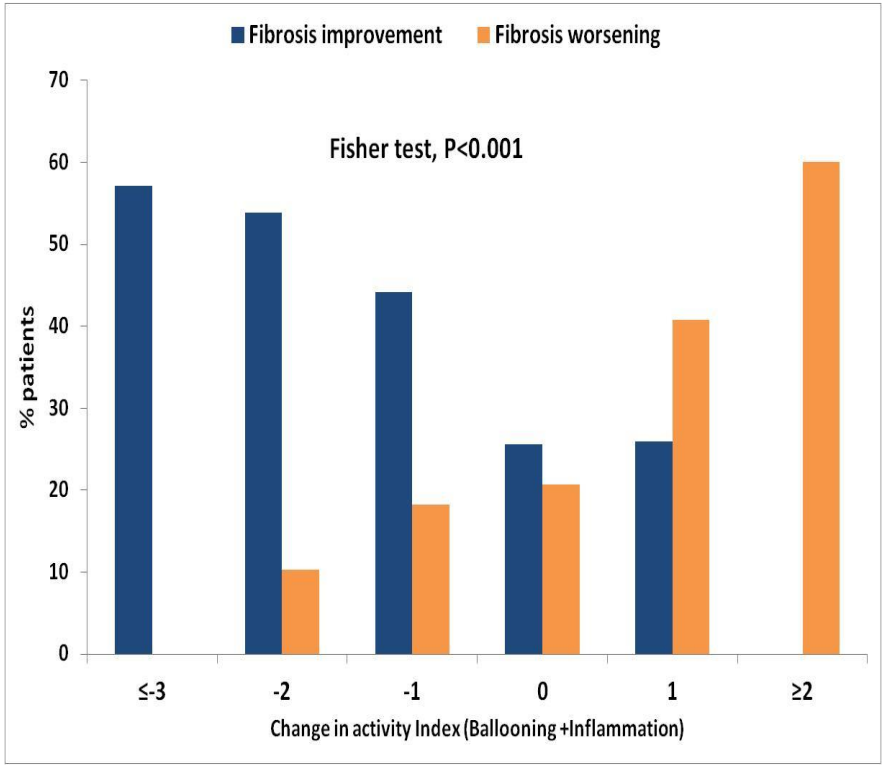
Brunt, Hepatology 2019

Changes in NASH activity index and fibrosis evolution

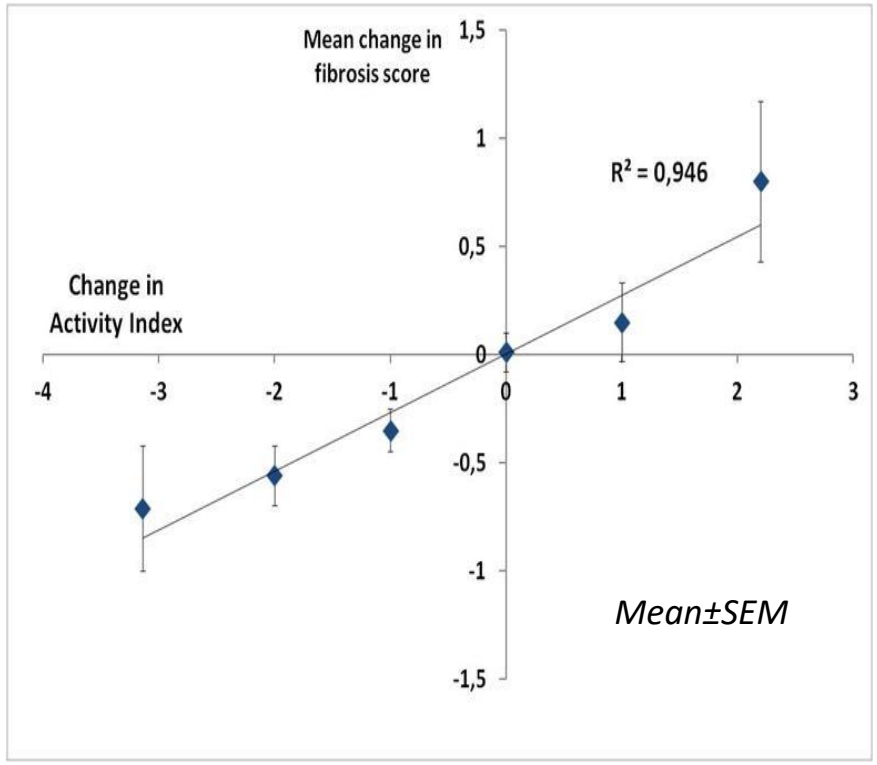
Activity Index : sum of scores for ballooning and inflammation

N=234

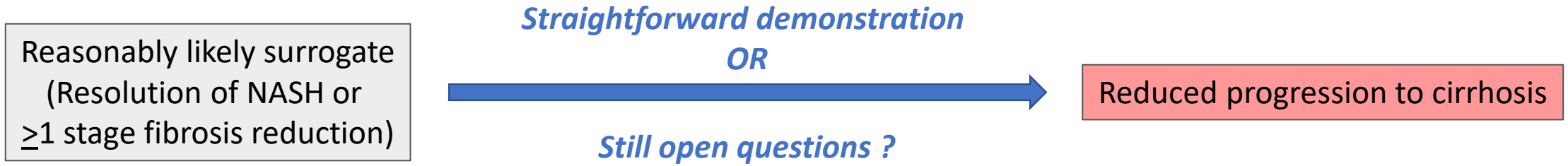
% of Pts with fibrosis change



Mean change in scores



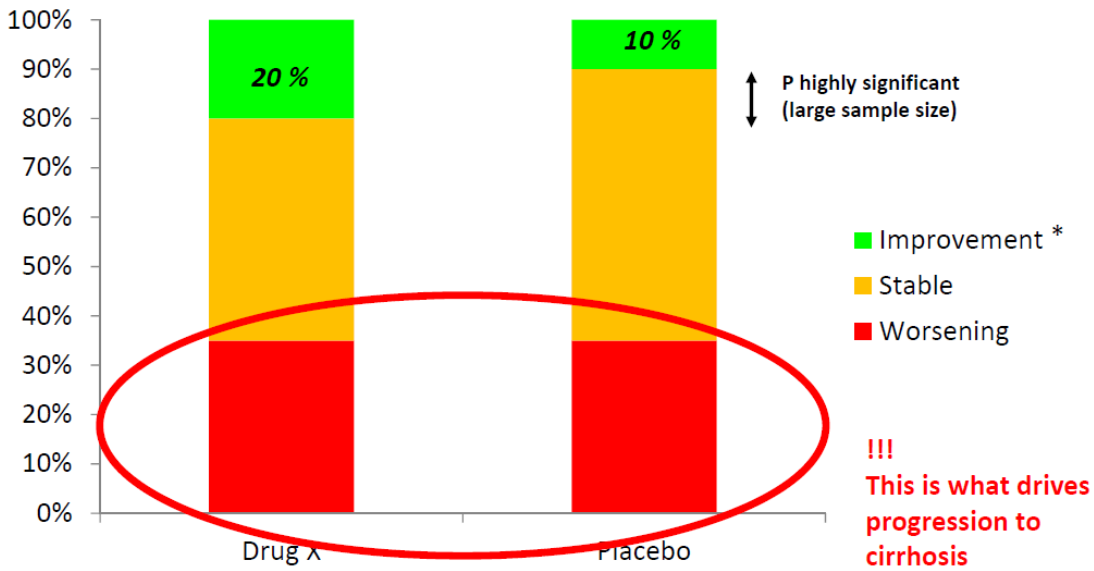

Business



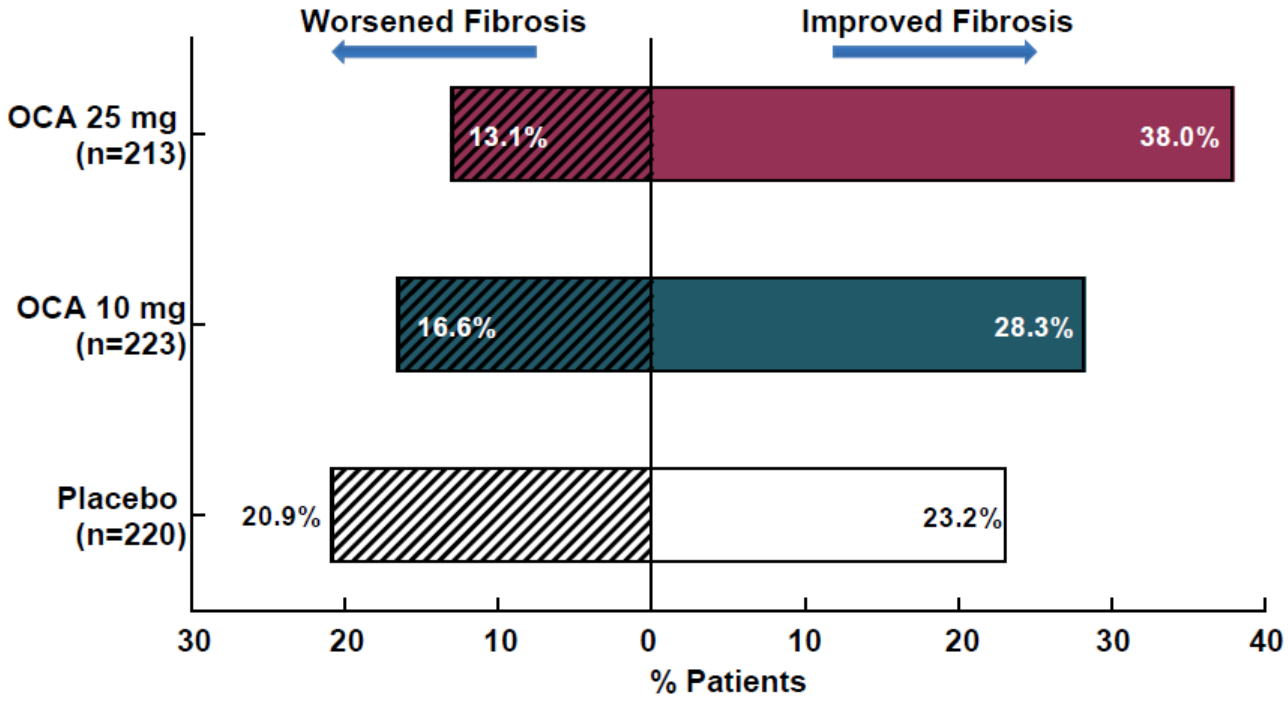
- Does improvement in disease activity predict less progression to cirrhosis to the same extent as NASH resolution ?

➡ Resolution of NASH **BUT** no effect on fibrosis ?

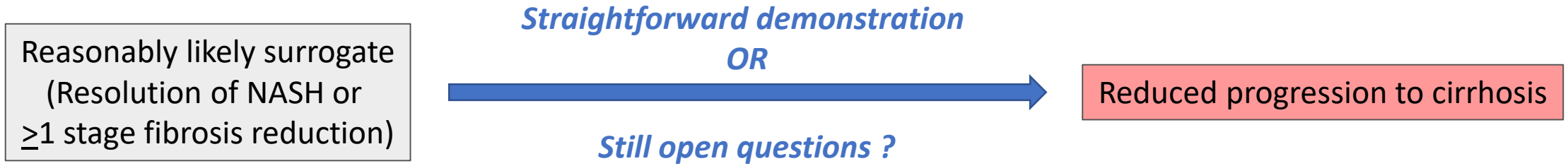
➡ Does ≥1 stage fibrosis improvement truly predict less progression to fibrosis ?



Ratziu, J Hepatol 2018



REGENERATE, ILC 2019



- Does improvement in disease activity predict less progression to cirrhosis to the same extent as NASH resolution ?
- Resolution of NASH **BUT** no effect on fibrosis ?
- Does ≥1 stage fibrosis improvement truly predict less progression to fibrosis ?
- If the interim analysis is successful, should the remaining patients still be biopsied at the interim time point ?
- How many times does this paradigm need to be proven ?

How will conditional approval change the current landscape?

- For trials
  - The demonstration of the predictive value of the likely surrogate
  - ➡ The need to continue the outcome trials
- For clinical practice

ISSUES WITH TRIAL RETENTION IN OUTCOME TRIALS

There is an approved drug …

No definitive proof of efficacy on relevant endpoints
Stringent methodological requirements necessary for all drugs

Assess the situation on an individual basis –
if a patient improves at the interim, continue !

Trial fatigue …

Simplified follow-up, but visits /3 months still necessary

Why continue in a non-responder ? …

Response may be slower in some patients (true for 12 mo interim analyses…)

What if I am on placebo ? …

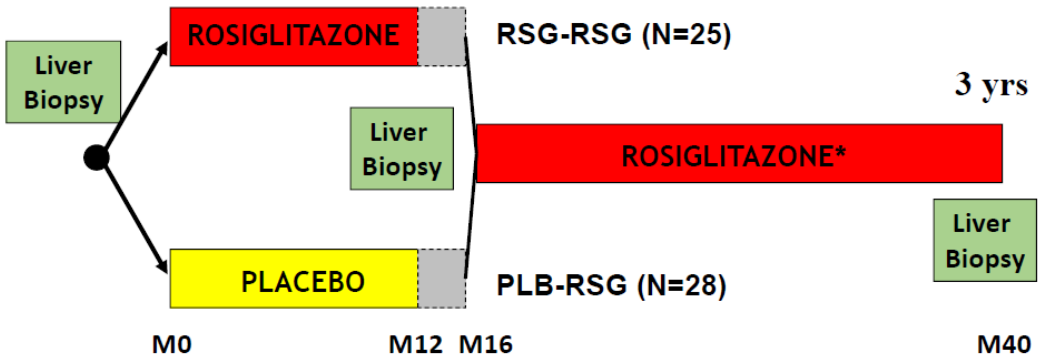
Progression to cirrhosis will not go unnoticed …
Lower chances of being on placebo (1:2 randomisation)

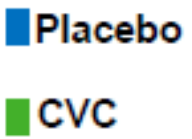
REASONS WHY COMPLETING OUTCOME TRIALS IS IMPORTANT

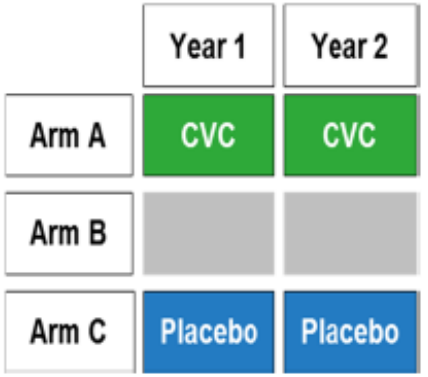
To validate the surrogate/for definitive approval

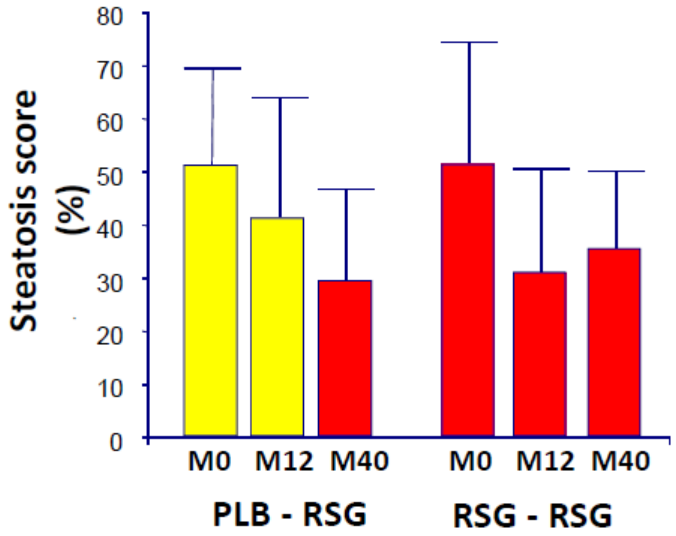
To justify long-term therapy

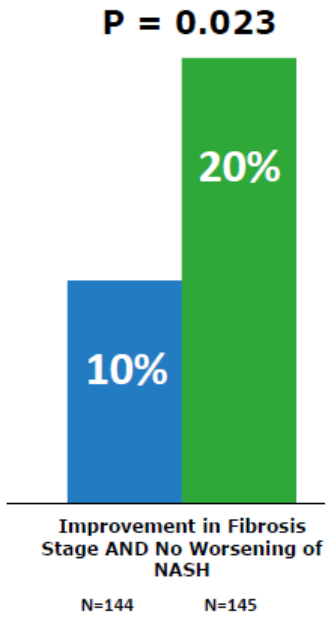
Can one year efficacy results be extrapolated to life-long therapy ?



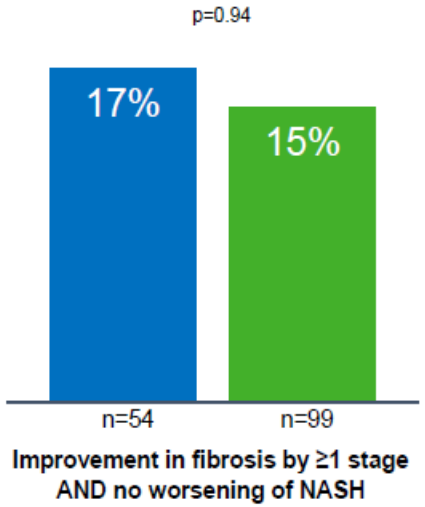








Year 1



Year 2

Ratziu, Hepatology 2010

Friedman, Ratziu*, Hepatology 2018*

Submitted

REASONS WHY COMPLETING OUTCOME TRIALS IS IMPORTANT

To validate the surrogate/for definitive approval

To justify long-term therapy

Can one year efficacy results be extrapolated to life-long therapy ?

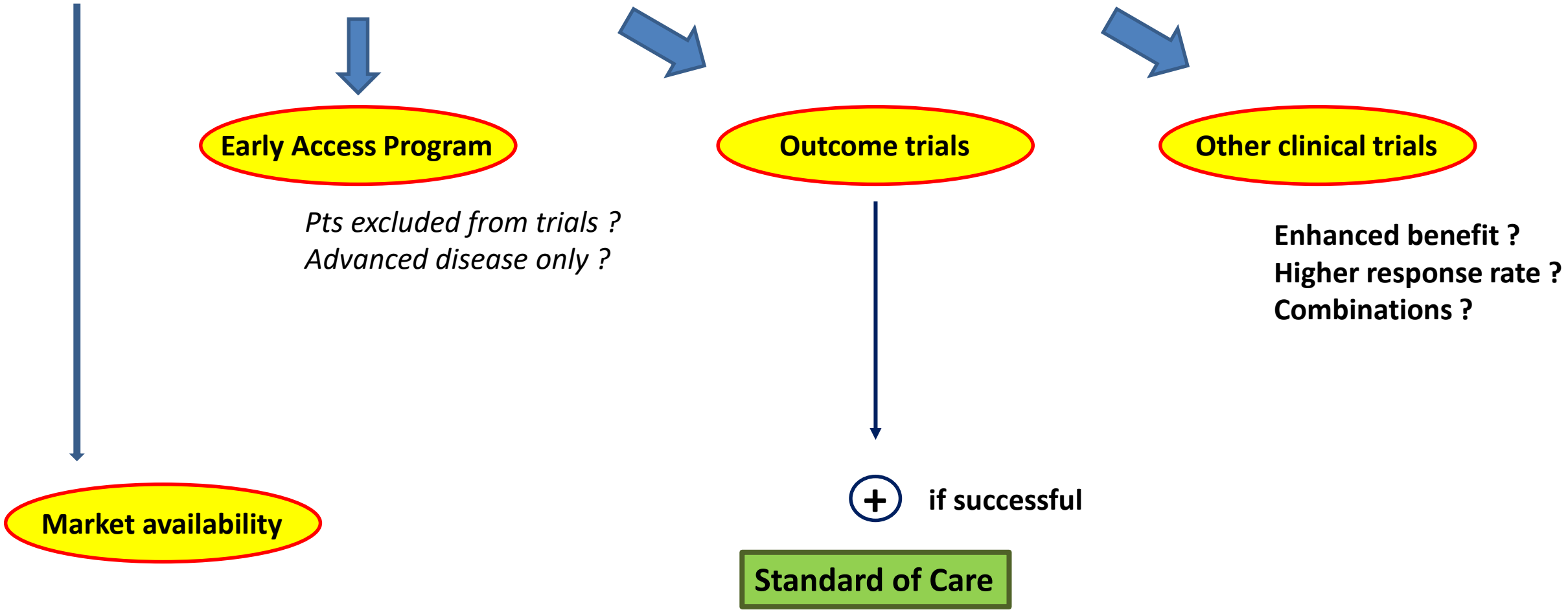
To understand the natural history (placebo arm)

How will conditional approval change the current landscape?

- For trials
    - The demonstration of the predictive value of the likely surrogate
    - The need to continue the outcome trials

➡ For clinical practice

LANDSCAPE AT TIMING OF CONDITIONAL APPROVAL



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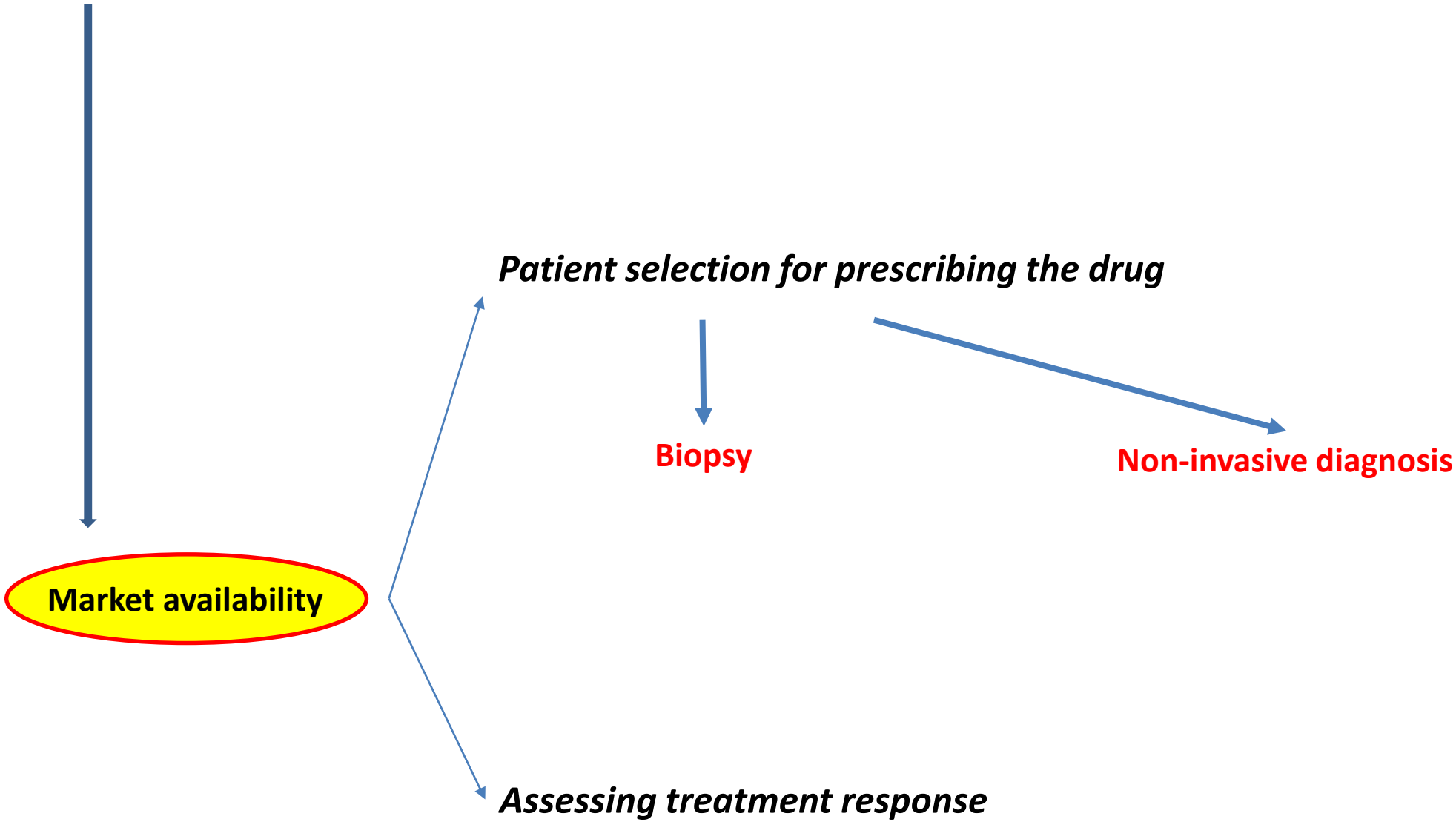

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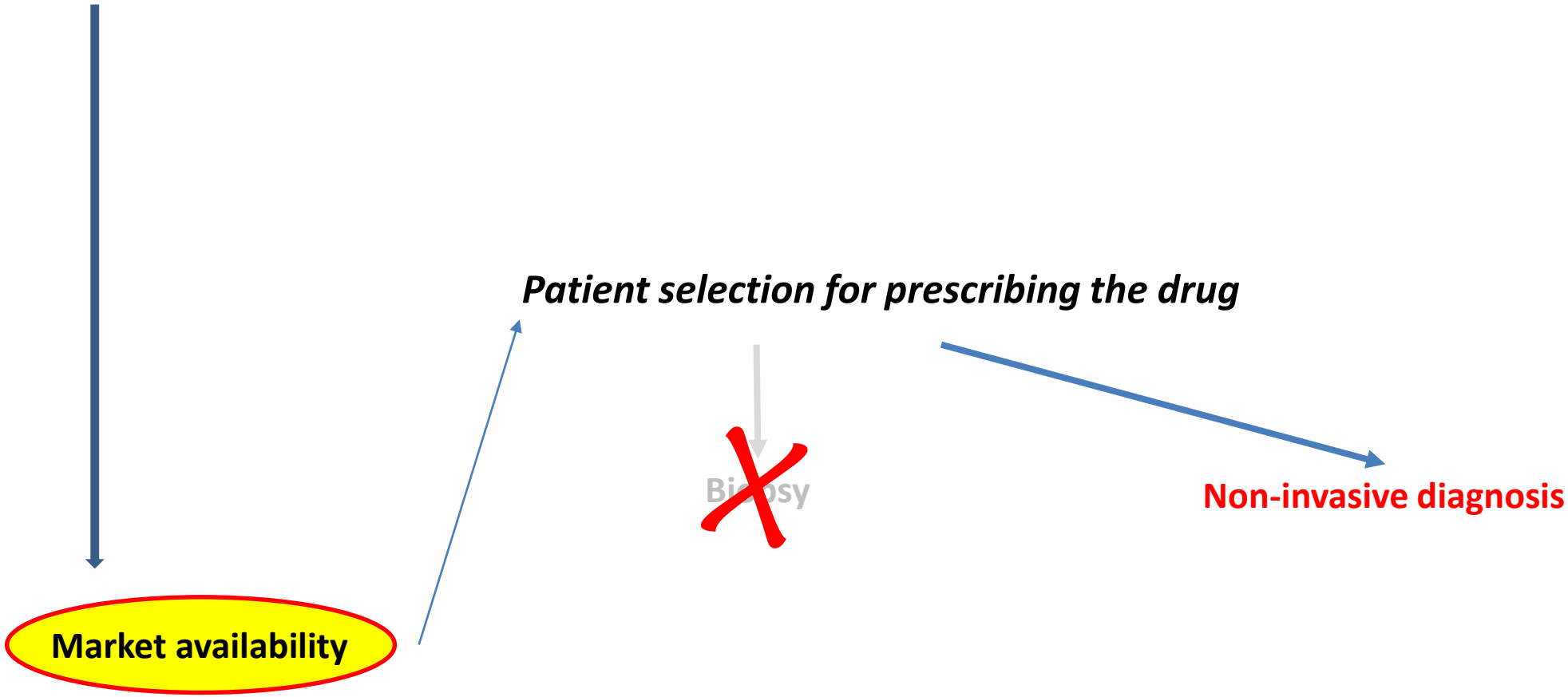


Selecting patients for therapy without liver biopsy !

- *NIS 4 (Genfit)*

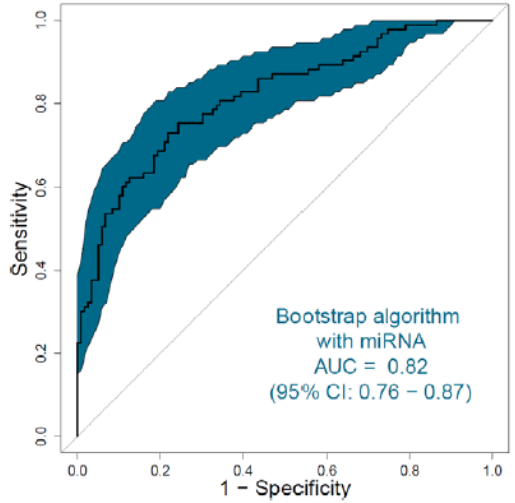
- **To-be-Treated (NAS≥4, F≥2) vs. Not-To-Be –Treated (NAS<4, F<2)**

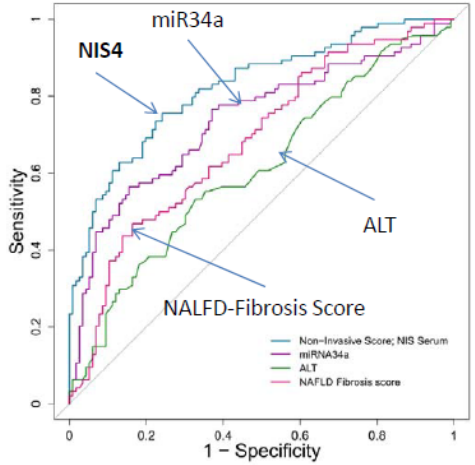
NIS4 includes: miR34a, Alpha2-macroglobulin, CH3L1 (YKL40) and HbA1C

Baseline data from GOLDEN and RESOLVE-IT trials (N = 714)

Training set: 220 patients from GOLDEN trial

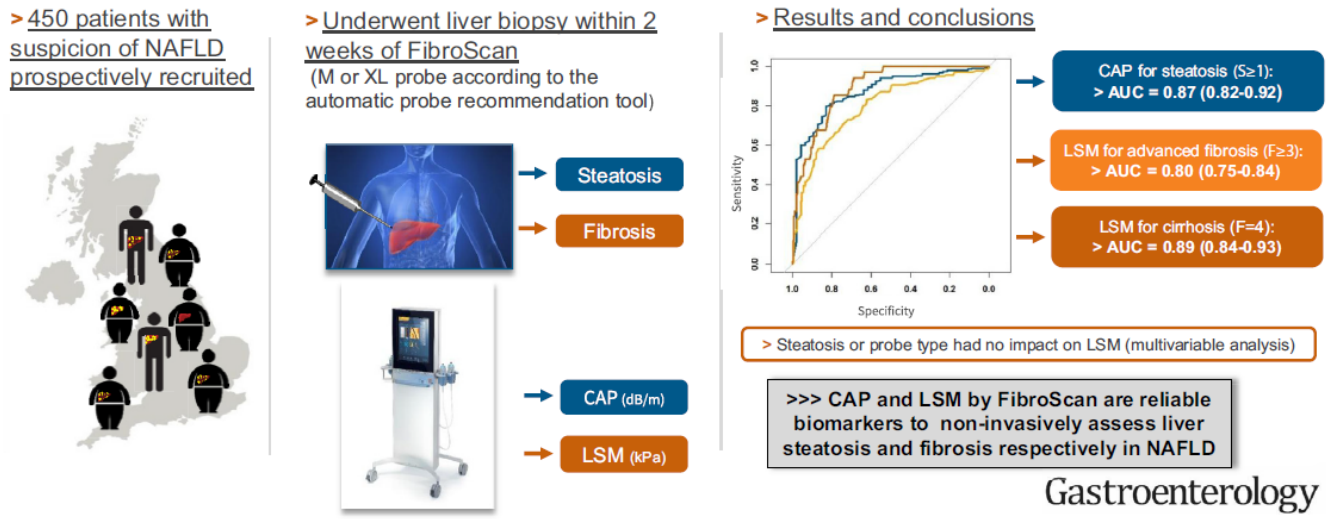
Validation set: first 467 patients screened for inclusion in RESOLVE-IT





Courtesy R Hanf, Genfit

- *Fibroscan-CAP-AST (Echosens)*



Eddowes Gastroienterology 2019
Newsome AASLD 2018

- *Clinical algorithms (ex Gilead AASLD 2018)*

Anstee AASLD 2018, Younossi AASLD 2018

LANDSCAPE AT TIMING OF CONDITIONAL APPROVAL

Patient selection for prescribing the drug

~~Biopsy~~

Non-invasive diagnosis

Market availability

Exceeding the limits of liver histology markers☆

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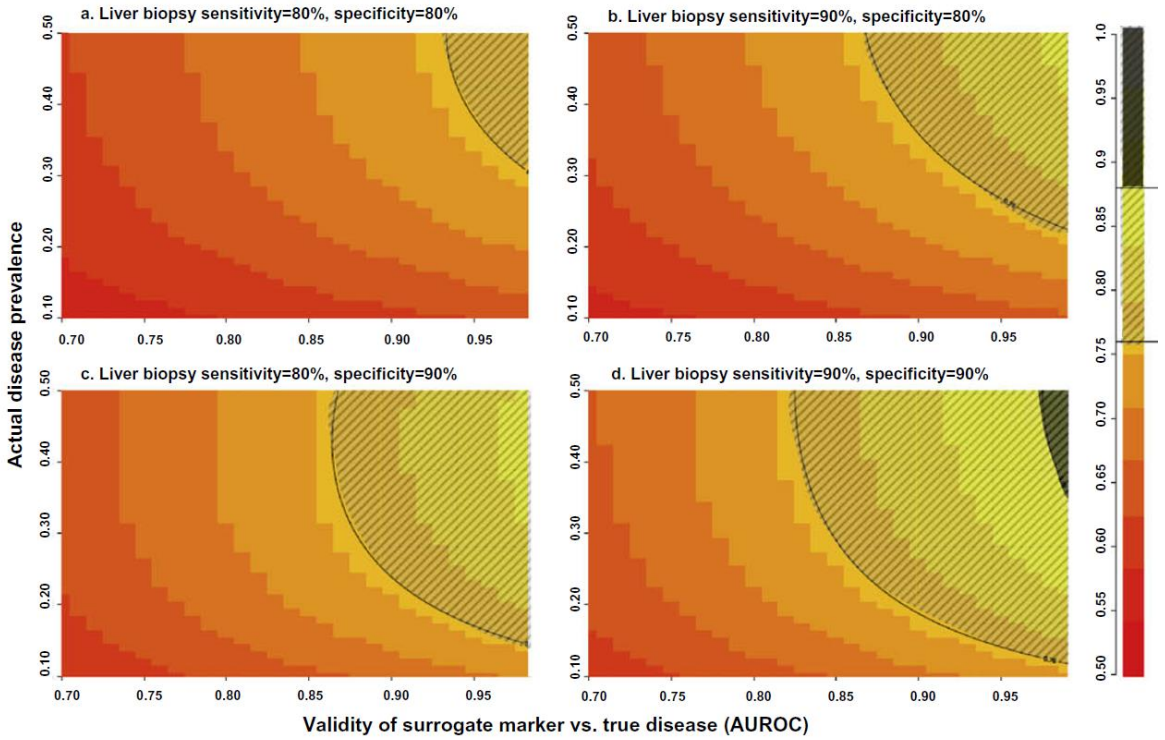
[2]*Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA*
[3]*Liver Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA*

AUROC the higher the better ??

***Results*: In the 'best' scenario where liver biopsy accuracy is highest (sensitivity and specificity of biopsy are 90%) and the prevalence of significant disease 40%, the calculated AUROC would be 0.90 for a perfect marker (99% actual accuracy) which is within the range of what has already been observed. With lower biopsy sensitivity and specificity, AUROC determinations >0.90 could not be achieved even for a marker that perfectly measured disease.**



Editorial

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Serum fibrosis markers: Death by validation or a leap of faith?

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See Article, pages 238–244

LANDSCAPE AT TIMING OF CONDITIONAL APPROVAL