**Forum for Collaborative HIV Research**
**Liver Forum Meeting #3**
**Summary of Proceedings**
Thursday, November 12, 2015
San Francisco, California

Meeting presentation slides and other background materials can be found here, under the heading Liver Forum #3: http://www.hivforum.org/projects/drug-development/liver-forum

**Session #1: Project Overview and Updates**
**Moderators:** Veronica Miller, Arun Sanyal and Gary Burgess

Welcome and Introductions:

- Veronica Miller welcomed the attendees to Liver Forum 3 and noted both the large attendance (138) and the number of new companies that have joined the Forum since the last meeting. She also acknowledged the role of the Liver Forum leadership in recruiting new members
- Dr. Miller took a straw poll of new attendees and noted the large proportion of those attending for the first time. She also observed that this is an indication of how rapidly the field is growing and of the importance of the role of the Liver Forum in helping to clarify the regulatory pathway for NAFL/NASH related therapeutics
- Taking note of the full house, Dr. Miller justified the "house rule" that no more than two representatives from any company can attend LF in person.
- With this third meeting, LF is officially one year old.
    - First meeting held in November 2014 in Boston, preceding AASLD
    - Second meeting held November 2015, preceding EASL in Vienna
    - Discussions held at these Forum meetings facilitate decision making regarding priorities for the coming year; mechanisms to use to achieve objectives; identification of problems and obstacles and how to overcome them
- The inauguration of Liver Forum was preceding in 2013 by the "famous" FDA-AASLD workshop
    - Report of that meeting recently published in Hepatology[1]
- Some of the hallmarks of the past year include:
    - Numerous contributions by private sector sponsors to support LF staff who coordinate the Working Groups, develop databases and provide administrative support for LF activities
    - Many of the LF member companies are smaller biotech start-ups. It's exciting to work with that type of energy
    - Excellent leadership provided by the LF Steering Committee. SC includes representation from
        - U.S. and European regulatory agencies
        - The pharmaceutical and biotech diagnostics industries
            - Industry representatives will now be serving on the SC on a rotating basis, with two year terms; in a staggered rotation
        - patient constituencies

[1] Hepatology. 2015 Apr;61(4):1392-405. doi: 10.1002/hep.27678. Epub 2015 Mar 19.

        - AASLD and EASL
        - Academic medicine
    - Acknowledgement of the contributions made by LF staff: Jeff Kaminsky, Myrna Cozen and UCB SPH interns, Lauren Smith and Aileen Artus
        - Much of the LF Working Group support is provided out of UC Berkeley, where Myrna and the interns are based
        - We encourage sponsors and other members to take advantage of LF activities to provide educational opportunities for interns and fellows
    - Grateful acknowledgment also made to Margie and Dave Poole, of Informed Horizons, who make all the logistical arrangements for LF meetings

Overall Goals of the Liver Forum:

- To be an independent and neutral venue for ongoing multi-stakeholder dialogue focused on the regulatory process for interventions and diagnostics
- To facilitate the best science-based decisions in real time regarding efficacy and safety
    - Break down inefficiencies in the regulatory process
    - Increase clarity
    - Provide benefit to the field

Today's agenda:

- Regulatory update: starting with this has become a tradition
- Reports from two Working Groups
    - Disease Definitions
    - Data Standardization
- Panel Discussion: non-invasive diagnostics
- Announcements
    - Existing collaborations
    - Plans for an IOM report on NAFLD/NASH
- This will be a scientific exchange and dialogue and discussion.
    - We encourage participants to "step out of the box" and be a bit provocative and "push the envelope"—that is the way to reach new ground and support innovative approaches
    - House rules:
        - What is said in the room stays in the room
        - Comments are not for attribution
    - Report of this meeting will be posted on Liver Forum website

Introductory Remarks: Arun Sanyal

- Welcome everybody to this third Liver Forum meeting
- It's been an incredible journey, over the past year, to see the growth and excitement in the Forum and the progress that has been made
- We will hear some interesting discussions today about harmonizing disease definitions, which is the first critical step—of many steps to come
- There have been inquiries from academics regarding how to get involved in the Liver Forum. To reiterate: the focus of the Liver Forum is to facilitate regulatory development for fatty liver disease and hepatic fibrosis
    - Focused on regulatory science and evidence burden that needs to be generated to move therapeutic development along the regulatory pathway
    - This effort does not replace the [basic, clinical science] that is presented at main liver meetings

    - We want to reach across the entire breadth and depth of expertise in the field of fatty liver disease and fibrosis, wherever it exists on both sides of the Atlantic
    - We do this via the LF Working Groups
    - Our goal is to be inclusive; that is a central theme of our mission ("our working mantra")
- Educational Spin-Off
    - Building capacity in terms of the next generation workforce: we are developing educational opportunities through our programs at UC Berkeley for people who want to develop a career in regulatory science [in general] and as it applies to liver disease
- Acknowledges UC Berkeley for providing us a home base and Veronica Miller for her superb leadership

Introductory Remarks: Gary Burgess

- There has been an enormous amount of work accomplished since the last meeting
    - Encouraging to see how the various streams of work are coming together
    - Informative to be part of the work and contribute
    - Encourages industry colleagues to get involved

Lara Dimick-Santos with updates from the FDA: **"Endpoints and Populations and Trial Designs for Clinical Trials in NASH Indications"** [Please refer to Dr. Dimick's slide presentation: http://www.hivforum.org/storage/documents/2015/Liver_Forum/LF3/ldimick_lf3%20final_regulatory%20perspective%20updates.pdf ]

- Populations needed for Phase 1 and 2 clinical trials
    - For early phase, proof-of-concept trials it's best to use patients with biopsy proven NASH but it's also acceptable to use patients who are just at high risk for NASH
    - For dose-ranging trials and Phase 2 trials that help inform Phase 3 trials, it's best to only target a population with biopsy proven NASH (NAS ≥ 4) and patients with liver fibrosis
    - The best target populations are those with liver fibrosis stage F2 and F3 (pre-cirrhotic) or perhaps F1 with risk factors. The FDA recommends staging fibrosis with NASH/CRN Brunt/Kleiner scale.
- Surrogate Endpoints
    - For early phase trials, endpoints should be based on the mechanism of the drug, and can consider using improvement in NAS and/or fibrosis scores. There isn't much evidence for using decrease in liver fat content as a marker.
    - For Phase 3 trials, the FDA would like to see complete resolution of steatohepatitis with no worsening of fibrosis as a composite endpoint.
    - Another acceptable composite endpoint for Phase 3 trials is at least one point improvement in fibrosis with no worsening of steatohepatitis
    - For phase 4 post-marketing clinical trials, primary outcomes will be largely clinical benefits outcomes.
        - For pre-cirrhotic patients, this will be histopathologic progression to cirrhosis. Histopathologic progression to cirrhosis will precede death, transplant or decompensation events, so it the most sensitive marker of clinical benefits.

        - For compensated cirrhotic patients, indirect measures of clinical benefit will be through death, transplant, decompensation events, and change in MELD score.
    - To use a surrogate marker, there must be a trial to verify that the surrogate actually does prove clinical benefit. These trials also need to be placebo-controlled since we don't know the real natural history of the disease.
- Approach to Planning for Clinical Trials
    - One package should be prepared in which the plans for the Phase 3 and Phase 4 trials and the statistical analysis are presented. Investigators should come in and discuss their plans with the FDA. There is guidance available for the statistical analysis. The FDA will then review all of this with investigators before they begin the Phase 3 trials.
    - When doing Phase 3 and phase 4 trials, investigators must divide the alpha. The FDA prefers two trials, but one trail can be utilized. The guidance outlines what is necessary depending on whether one or two trials are planned.
    - An alternate approach is to plan ahead from the Phase 2 stage. Sponsors can submit a proposal to enroll patients in a Phase 2 trial and then roll them over into Phase 3 and phase 4 trials. This takes a lot of pre-planning, but it can save time and money. The whole plan must be submitted before the Phase 2 trial begins.
    - Usually sponsors need two well-designed trials to support a marketing application, but sometimes if a single trial is large and has robust and persuasive data, a single trial may provide enough evidence of effectiveness so that only one trial is needed.

Elmer Schabel, MD with updates from the EMA: **"Regulatory update from Europe: Procedures to promote early access of medicinal products to the market"** [Please refer to Dr. Schabel's slide presentation: http://www.hivforum.org/storage/documents/2015/Liver_Forum/LF3/lf3%20final_eschabel_regulatory%20perspectives%20updates.pdf]

- Current tools for early access – both tools have been updated this year
    - Conditional approval
        - The medicine fulfills an unmet medical need, targets a seriously debilitating or life-threating disease, the benefit-risk balance of the product is positive, and comprehensive data is expected to be provided after authorization. The objective is early authorization on the basis of less complete clinical data.
        - Details about application process on slide #5 and 6
        - Details about new updates on slide #7
    - Accelerated assessment
        - Medicine is of major interest from the view of public health and the viewpoint of therapeutic innovation. The objective is a faster assessment of marketing authorization application (reduces assessment time from 210 to 150 days).
        - Details about new updates on slide #9
- Initiatives to improve early access ***Slide # 10 – page 21***
    - Adaptive pathways approach
        - A pilot project developed in March 2014 to create an iterative development plan for trials that are already ongoing. This would allow ongoing, early phase projects to discuss their current "live assets" and involve different stakeholders to try to potentially explore and develop new pathways. This creates a safe harbor for brainstorming. Sponsors

who want to participate must have drug candidates that meet an unmet medical need, evidence for positive benefit-risk balance, commit to widening the population of the drug targets, etc.
    - PRIME ("proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines")
        - A project started in June 2015 whose aims are to create better informed development plans, improve the quality of marketing authorization applications, promote regulatory awareness, reinforce early dialogue and provide regulatory support to stimulate innovation, optimize development, and enable accelerated assessment of priority medicines. Medicines must meet the criteria for accelerated assessment to be eligible for PRIME. PRIME offers scientific advice from multiple stakeholders, early assignment of rapporteurship, and early decision on accelerated assessment.
- Conclusion: There are differences between the EMA and the FDA, and there are new changes within the EMA (PRIME, Adaptive pathways, etc.). Talk to regulators early.

Andrew Mulberg - **An evolving partnership model for rational drug development: applications to liver diseases** [Please refer to accompanying slides: http://www.hivforum.org/storage/documents/2015/Liver_Forum/LF3/lf3%20final_amulberg_regulatory%20perspectives%20updates.pdf ]

- The key principles to rational drug development are defining the disease, assessing the natural history, identifying assessment tools (including biomarkers, etc.), and developing an outcome measure (whether it be one for accelerated approval or for clinical benefit). The Liver Forum is really working on addressing all of these critical steps. Definitions need to be clarified, etc. Collaboration is key. The patients suffer if we don't work together.

**Session #2: Disease Definitions Working Group**
**Moderators:** Stephen Harrison and Sophie Megnien
(Please refer to the accompanying slide set: http://www.hivforum.org/storage/documents/2015/Liver_Forum/LF3/lf3%20final_disease%20definitions%20wg.pdf )

Introductory comments by Veronica Miller

- The overall goal for this Working Group was to facilitate drug and diagnostics development by deriving consensus on disease definitions
    - Specifically to distinguish patient populations for the purpose of clinical trials for regulatory approval
    - Mandate: evidence-based review of definitions
    - Process: deconstruct and reconstruct and "don't be shy about it"
- It evolved out of the first Liver Forum meeting when we realized that people in the field were using varying definitions for stages of NAFLD and NASH
- Sophie Megnien and Stephen Harrison have led this working group, which, after much discussion, was divided into seven subgroups.
    - The disease stages or categories were intended to be debated and discussed. This was a fluid process, with the outcome intended to inform future clinical trial design for NASH
    - We may decide these are not the right subcategories, but that is what this process is all about

        - Pushing the envelope to do something we've never done before
- Joel Lavine and Miriam Vos were invited to provide input from the pediatric perspective
    - We will activate the Pediatric Working Group in the period immediately following this meeting
    - At the next Liver Forum meeting, we will integrate their input into these definitions
- Leading pathologists, Pierre Bedossa and David Kleiner, provided input to definitions of each stage and to the overall conceptualization scheme
- The outcome of this process will facilitate assessing the role of new, non-invasive diagnostics
- Once this process is complete, it will help us develop benchmark criteria for clinical trials and clinical/biomarkers for natural history studies

Process Description by Myrna Cozen [Please refer to slide set for a detailed overview of the process: http://www.hivforum.org/storage/documents/2015/Liver_Forum/LF3/lf3%20final_disease%20definitions%20wg.pdf]

- Process described as a case of orchestrated chaos that worked beautifully
- Started by deconstructing this disease entity knowing full well that there might be controversy about the categories we chose
- The seven subgroups and their respective leads are as follows.
    1. Isolated Steatosis: Manal Abdelmalek
    2. Indeterminate NASH: Stephen Harrison
    3. Definite NASH without Fibrosis: Quentin Anstee
    4. NASH with early fibrosis: Vlad Ratziu
    5. NASH with advanced fibrosis: Laurent Castera
    6. NASH with compensated cirrhosis: Scott Friedman
    7. NASH with decompensated cirrhosis: Brent Tetri
- Each subgroup corresponded to a proposed stage of disease.
- Each stage was to be characterized with regard to the following criteria:
        - Histologic phenotype
        - Disease activity
        - Fibrosis stage
        - Clinical phenotype
        - Non-invasive diagnostics—to the extent that data is available
- Working group members were assigned to one of the seven subgroups; each was to work toward a consensus definition of their respective stage, using the above criteria
    - Subgroup members were also assigned to identify research gaps and to recommend key references to support their recommendations
    - Each subgroup member was given a blank template—a discussion document—on which they were to provide their written input into these categorical definitions
    - These contributions were collated and a subgroup conference call followed
    - Lively and exhaustive discussion of each disease category ensured, which allowed for the overlap of categories and the questioning of this particular framework
    - Areas/issues that need further elucidation were identified
    - Preliminary results have been collated, edited and assembled into the composite table that has been distributed
- It should be noted that FDA representatives were present on every call and that their requirements for NASH clinical trials are reflected in the preliminary table

- An alternate approach is to juxtapose our proposed categories along two axes: metabolic vs. fibrotic, as proposed by Brent Tetri for purposes of discussion. (See slide 11 of the "Data Standardization Working Group Progress Report" presentation)
    - The purpose of the graphic is to point out how heterogeneous NASH is
        - it is possible to have a high NAS score, but not have significant fibrosis
        - other patients might fibrose very easily with just a little steatosis, but their disease may progress rapidly
    - NASH does not always or necessarily progress sequentially
- The disease defining process will continue with input from pediatricians and pathologists
- It will culminate with the publication of two or three manuscripts, reflecting the process and the outcome
- The following research gaps were also identified (see slides 14-15 of the "Data Standardization Working Group Progress Report" presentation)
    - Overall Need for Natural History Studies: large scale, longitudinal studies are called for, especially those including patients with repeat biopsies
    - Identification of Risk Factors for Disease Progression
        - Simple or isolated steatosis  NASH
        - •Indeterminate NASH  Definite NASH with and without fibrosis
        - •Bridging fibrosis  cirrhosis
        - Compensated cirrhosis  decompensated cirrhosis
    - Further elucidation of the etiology of NASH
        - Risk factors for metabolic NASH versus non-metabolic forms of the disease
        - What are acceptable levels of alcohol consumption to still be considered NASH?
    - Studies needed to determine whether biopsy still required for definitive diagnosis of both early and late stage NASH
        - Are imaging technologies sufficiently reliable that they can be used to replace biopsy?
        - Are specific biomarkers far enough along in development that they can be used in combination with imaging for definitive diagnosis?
        - Is there a staging system (e.g., NAS or SAF) that can be used with confidence in clinical diagnosis, natural history studies and as outcome measure for clinical trials?

Disease Definitions Subgroup Reports and Summary Discussions (Sophie Megnien and Stephen Harrison) The Disease Definitions Summary Table to which these discussions refer is currently in revision and will be made available with our final set of recommendations in Spring 2016. These reports reflect the discussions that took place in each subgroup, beyond those establishing consensus on the categorical definitions. Introduction: This is the first step, a starting point.

- We still have some overlap between the categories, so more refining of the definitions still need to be made
- We need to identify the characteristics of individuals within each category that put them at risk of progression—this work can be done only after we reach consensus on these definitions

- Subgroup 1: Isolated (or simple) Steatosis (Manal Abdelmalek)
    - We readily came to agreement on histologic phenotype: $\geq$ 5%steatosis on liver biopsy without any evidence of necroinflammation, lobular inflammation, ballooned hepatocytes with fibrosis stage 0

- The question arose: would minimal lobular inflammation of just one or two points qualify as simple steatosis (within the context of the above)?
- Characterized by macrovasicular steatosis with or without microvesicular steatosis of any zonality;
    - However, microvesicular steatosis in the absence of macrovesicular steatosis would raise a flag for an etiology other than metabolic syndrome/obesity related fatty liver disease; e.g. mitochrondiral dysfunction, LASD, etc.
- Low risk clinical phenotype
    - With fibrosis stage 0, this clinical phenotype would have no associated liver related outcomes that would be of pertinence to a clinical trial
    - Majority of patients would be insulin resistant; all would have hepatic insulin resistance
        - One may not see the ATP-3 criteria fulfilled
        - Patient may still have hepatic steatosis in the absence of diabetes, increased waist circumference or hypertriglycemia
    - Best not to be too specific with regard to weight categories: we could certainly see simple steatosis with normal weight or anywhere along the weight spectrum
        - However true lean phenotype would raise questions about alternative etiology for the presence of steatosis
- Simple steatosis, based on clinical phenotypes, should be a definition that is based on exclusion of secondary variables, including alcohol, certain medications that are known to precipitate steatosis or other metabolic conditions like Wilson's disease or LASD
- We did not describe and struggled with what the threshold of alcohol should be to define this phenotype
    - Some on the panel though we should lower the bar; others though it should be a little bit higher than 20 grams/day for women and 30 grams/day for men
    - In order to be relevant to the population at large, we elected to keep these threshold amounts and considered them appropriate for a working definition
- With regard to children:
    - Children greater than two years of age could have simple steatosis, but a truly lean child with a lean Z-score would suggest other diagnoses
    - The clinical phenotype would not be characterized biochemically or based on glucose, lipids or other (typical) parameters, because they may be normal in the presence of simple steatosis or anywhere along the spectrum of abnormality
    - The sensitivity of radiographic or biochemical markers is too poor to use to define simple steatosis in children
        - Did not dismiss the pertinence of sensitive radiographic measures for assessing changes over time (by MRI, CT or US)
        - No clear biomarker has been validated thus far

- Subgroup 2: Indeterminate NASH (Stephen Harrison)
    - Much of what was described for Simple Steatosis, in terms of disease activity, fibrosis stage, non-invasive diagnostics, etc., also applies for indeterminate NASH

- Ultimately, this was thought to be a "wastebasket" term for everything that "just wasn't NASH"
  - No convincing ballooning
  - From a regulatory perspective, it is not NASH; it's everything but NASH
  - Additional problem: Biopsy is an imperfect gold standard
    - Multiple samples from same biopsy can yield differing results with regard to ballooning, inflammation, fibrosis, steatosis
- Focus on what this category is from a regulatory perspective
  - Is there a difference between simple steatosis and indeterminate NASH?
    - If yes, then keep this category separate
    - If no, then from a regulatory perspective, perhaps we should "parse this out" and say, "this is just purely steatosis and nothing else is going on" or this is steatosis with a little mild inflammation
  - Caveat to consider: the notion of steatofibrosis without ballooning
    - Fat, a little bit of inflammation, more portal-based, fibrosis, but no ballooning
    - This phenotype might have a different natural history than determinate NASH with no fibrosis
- Offered up to discussion by the larger group: can we combine non-NASH steatosis together with indeterminate NASH? Or do we not have enough natural history data to do that [this was a recurrent theme in discussions throughout the session]
  - Some data show that steatosis has a different natural history than steatosis with inflammation; however the studies are small and there is inherent selection bias
  - Probably not enough longitudinal data to separate these two categories
- With regard to children:
  - This indeterminate category has a very pertinent applicability to children
    - Sometimes called indeterminate borderline zone 1 or borderline zone 3
    - A significant subset of children have borderline zone 1 pattern, that can include:
      - very high ALT (300-400)
      - Cirrhosis with portal bridging
      - No ballooning
      - No lobular inflammation, but with portal inflammation
  - By pathologists' definition of adult NASH, these children do not have adult NASH, but certainly they have a clinical course that can be rapidly progressive to cirrhosis
    - Seen this numerous times in children as young as eight years
    - This fits the "indeterminate" category, but is a specific type and it is important to keep the designation of it being NASH—an alternative form of NASH
  - It's also important to invoke the Pediatric Research Equity Act (PREA) in this context and remind ourselves that every Phase 3 trial in adults has to have a plan for a pediatric trial

- Subgroup 3: Definite NASH without fibrosis (Quentin Anstee, with additional comments by Pierre Bedossa)

- This is quite an interesting category and arguably represents a key bridge in the pathogenesis of NASH. Many opinions were expressed during the course of our conference call
  - On one side [of this category], we're looking at the distinction between steatosis and steatohepatitis
  - On the other side, we're also looking at the absence of fibrosis
- In terms of histological criteria, there was consensus that the presence of ballooning was a touchstone for evidence of the commencement of steatohepatitis
- In terms of disease activity, there was much discussion about the relative merits of two histological scoring systems currently in wide use:
  - The NASH CRN, modified Brunt scoring system
  - The FLIP SAF score, which has currency in Europe and which is perhaps more sensitive in detecting disease activity
- The group questioned the distinctions between steatosis, steatosis with minimal inflammation and NASH, in terms of risk of disease progression and asked whether disease categories 1, 2 and 3 could, in some ways, be combined.
- This lead to further discussion about sampling error in biopsy, both in terms of detection of ballooning and the presence of any fibrosis
- In terms of clinical phenotype, there is not a single symptom profile associated with the presence of steatohepatitis.
  - The more features of metabolic syndrome an individual possesses, the more likely they are to have steatohepatitis
  - In particular the severity of insulin resistance is a key marker for that
- Regarding non-invasive testing, the consensus was that at present there are not good non-invasive tests that have robust evidence for utility at diagnosing steatohepatitis
- Dr. Bedossa made three major points in response to the Subgroup 3 presentation, but which apply more generally:
  - He addressed the comparison between the NAS and SAF scores:
    - NASH is a combination of steatosis, inflammation and ballooning
    - In the NAS, there are three points for steatosis, three for inflammation and only two for ballooning
      - So ballooning, which is probably the most important lesion comprises only 25% of the total NAS score
    - In the SAF score, we eliminated steatosis, but included two points for ballooning and two for inflammation, so ballooning comprises 50% of the activity score, which gives more weight to this lesion, which is important
  - He expressed "no worry" with regard to sampling error in the context of NAFLD
    - There is a difference from [lesions seen in] chronic viral hepatitis, at least in the beginning, which can be very heterogeneous
    - NAFLD is very systematized, meaning that every zone 3 of the lobule, every area around the central vein is usually attacked with steatosis and with lesions; there is less heterogeneity
  - With regard to steatofibrosis (steatosis with fibrosis, but without NASH): it's 10-15% (of the cases we seen) and we probably will see more and more of these lesions, especially after treatment

            - If you address NASH effectively with treatment, NASH will disappear, probably leaving some steatosis and fibrosis (which probably takes more time to regress)
            - This is not NASH, but this is not simple steatosis and prognostic importance of this lesion is still significant

- Subgroup 4: NASH with early fibrosis or F1 fibrosis (Vlad Ratziu)
    - We all know how to diagnose clear cut NASH; we all know how to diagnose F1 fibrosis
    - Within the larger population of people with well-defined NASH and F1 fibrosis, there will be some with very active disease and within that group are those who are more likely to progress—those that fit the profile of rapid progressors
        - These are the patients that need to be treated
        - They need to be identified
        - Characteristics of this high risk group:
            - High SAF score; meaning activity, ballooning and inflammation
            - Clinical phenotype that is associated with progression: heavy metabolic syndrome, type II diabetes, worsening of the metabolic features and high HOMA IR and increased ALT
        - Therefore, rapid progressors can be defined as patients with active disease histologically or with the above clinical phenotype
    - FDA perspective is to be very specific with regard to how fibrosis is characterized. They recommend avoiding use of terms like early fibrosis or advanced fibrosis and instead use the term NASH with fibrosis and then designate F1, F2 or F3
        - This may suggest that it is not necessary to distinguish between NASH with early fibrosis and NASH with advanced fibrosis [note this implies collapsing subgroups 4 and 5)
    - With regard to the NAS, many sponsors are already setting their minimal inclusion criteria for clinical trials as a NAS $\geq 4$;
        - That could be three points for steatosis and one for lobular inflammation
        - That's very different that one point for ballooning, one (or two) for steatosis and one for lobular inflammation
        - Where do these variations in score belong for the purposes of clinical trials research?
    - It is also important to separate the diagnosis of steatohepatitis from the NAS or SAF score associated with it

- Subgroup 5: NASH with Advanced Fibrosis or F2/F3 Fibrosis (Laurent Castera)
    - This is the easiest group and clearly the target population for trials, as fibrosis is the strongest predictor for morbidity and mortality from NASH
    - Within the context of this category, there was also some discussion of scoring systems: NAS versus SAF
    - Regarding the clinical phenotype, most agree that there will be metabolic syndrome present
    - Other etiologies should be excluded: alcohol especially.
        - This may be an issue in France and the UK because many patients have both NASH and ASH
    - Regarding non-invasive diagnostics,

        - No imaging technique currently available is able to diagnose NASH (with fibrosis)
        - Regarding biomarkers, while there is some evidence on the utility of CK 18, it is not widely used in the U.S.
            - No other biomarkers are known to diagnose NASH
        - It is appropriate to measure liver stiffness in this setting
            - Fibroscan is widely used because it is easy to use in clinical practice
            - It is a better technique at ruling out than ruling in severe fibrosis and cirrhosis
    - Bridging fibrosis is the hallmark of this category, so that is F3 fibrosis
        - It is not always easy to distinguish F3 (bridging) from F4; again this may be due to sampling error

- Subgroup 6: NASH with cirrhosis (Scott Friedman)
    - For compensated cirrhosis, that is cirrhosis without any decompensated clinical events, our task here is very easy and is reflected in the summary table
    - What do we need to establish a diagnosis of cirrhosis non-invasively, as this is how we are most likely to identify patients for clinical trials?
        - Fibroscan alone is not sufficient
        - The clinical phenotype is easy: they have not had a decompensating event; aside from encephalopathy, there's little hemorrhage
            - Patients with portal hypertension, an elevated HVPG, are at greater risk for decompensation, but from a categorization perspective, that information would not be routinely available
        - Generally, you do not want to put a cirrhotic patient through a liver biopsy
        - For a clinical trial, we need to clearly define what we need from non-invasive diagnostics to establish a diagnosis of cirrhosis from the regulatory perspective
    - While we are [still conducting] biopsy-based trials, let's gather sufficient data from non-invasive diagnostics to establish what are the markers and cut-off points for cirrhosis
        - Fibroscan, being the leading diagnostic tool, currently
        - Ultimately these markers will supplant biopsy in later generation trials

- Subgroup 7: NASH with decompensated cirrhosis (Brent Tetri)
    - Issues related to decompensated cirrhosis mostly have to do with setting exclusion criteria for trials: decompensated patients will not be enrolled in clinical trials for NASH (i.e., those testing anti-fibrotics; at least not at present)
    - How we define decompensation is not always clear
        - Someone who has small varices, but no ascites and no encephalopathy—does that constitute decompensation?
        - We need to decide—one way or another—because what we decide will effectively include or exclude these "borderline" patients from clinical trials
    - We often don't have histology with these patients.
        - Most clinicians would agree that a patient who presents with nodular liver and platelets $\leq$ 80,000, are cirrhotic; we don't need to biopsy unless we are uncertain of etiology and want more information, so histology may or may not be available for that definition of the decompensated cirrhotic

Discussion topics, questions and comments raised and discussed throughout the panel reports)

- Much discussion ensued throughout the remaining panel presentations about the distinction between simple steatosis and indeterminate NASH.
    - Question was raised as to what would comprise resolution of indeterminate NASH: is it complete resolution of steatohepatitis?
    - Proposals were made to combine categories 1 and 2 or 1,2 and 3
- It is important that we take care in defining pediatric NASH not only for the purposes of clinical trial development, but also because of insurance coverage issues; if the standard definition for this disease in children is not what is traditionally considered NASH, there may be problems down the road with regard to insurance coverage for these conditions in children
- It is important to be constantly clear that the purpose of this discussion to define the disease stages for the purposes of clinical trials and not for clinical practice
- We are probably dealing here with very heterogeneous disease and when we conduct clinical trials, we need to work to obtain data on additional markers to better understand how/why people get this disease
    - NASH itself is a nebulous thing and might be multi-factorial in its underlying causes

Summary (Stephen Harrison)

- It is unprecedented to have this growing group of people come together to debate the different stages of fatty liver disease and we've made log-fold changes from where we were toward where we are going.
    - We've made a lot of progress
    - We still have a long way to go
- The enthusiasm and passion for getting rid of indeterminate NASH (and classifying everything that is not NASH as not NASH), especially among our French colleagues here, are apparent and appreciated.
    - This is a topic that we will need to revisit
- Joel's elegant comments about how children are different are notable.
    - The way we evaluate them certainly is different
- Quentin had a great idea about having a universal standard of care (and how that should be applied to the placebo arm patients across all trials)
- Pierre and other brought up the need to deal with steatofibrosis as a related entity that somehow needs to be brought into the classification schemed
- We also need to define cirrhosis clinically for the purposes of clinical trial eligibility
- The future of transcriptomics is very important to this venture and the direction we take in the future
- The idea of changing terminology to indicate NASH with or without fibrosis and specifically designate the fibrosis stage is also important
- Come to consensus on what we consider standard of care for the placebo arm and carry that forward universally in our trials; that would be a huge step
    - that will make it easier to use a pooled placebo arm as a single harmonized cohort

**Session #3: Data Standardization Working Group**
**Moderators:** Andrew Muir and Joanne Imperial

Introduction (Veronica Miller):

- To foster drug development, a robust, longitudinal cohort is required to elucidate the natural history of NASH and provide the biomarkers that we currently lack. To get to that

point, we tasked a Working Group to look at data currently being collected by NAFLD/NASH clinical trials and develop recommendations for a standardized set of baseline data that could be adopted across trials.
    - Standardizing the data collected at baseline in clinical trials would make the patients enrolled in the placebo arms of these trials an ideal potential cohort for a longitudinal, non-interventional natural history study of NASH
    - Another element would be to standardize the "standard of care" used for all patients enrolled in such trials, including the placebo arm.
- Overall goal for this Working Group: To facilitate the process of validation and acceptance of non-invasive diagnostics
- Strategies:
    - To put together a placebo arm based natural history cohort
    - Create a guidance or recommendations for baseline data for NAFLD/NASH clinical trials with the intention of increasing the comparability of data across trials
- Mandate:
    - Assess and compare baseline data from recently completed and ongoing studies
    - Make recommendations to improve comparability of data across studies

Process (Lauren Smith) [Please refer to slide set for details: http://www.hivforum.org/storage/documents/2015/Liver_Forum/LF3/lf3%20final_data%20standardization%20wg.pdf]

- We created a search tool to find all fatty liver disease related clinical trials in the ClinicalTrials.gov database, restricting the results to placebo-controlled, phase 2, 3 or 4 trials of drugs or biologicals
    - Search term included conditions such as metabolic syndrome, type 2 diabetes, obesity, etc.
    - Outcomes needed to include liver-related endpoints
- ClinicalTrials.com database does not include outcome measures, but does describe inclusion/exclusion criteria and outcome measures, as provided by sponsor
- Approximately 60 such studies were found that fit criteria; approximately 24 were studies conducted either by Liver Forum members or NIDDK
- Reviewing only these 24 studies, we found considerable heterogeneity in every eligibility criterion
    - Broad spectrum of target populations, with varying age ranges, mostly adult, mostly ages 18-75, but with wide variability
    - 20 studies required baseline liver biopsies, but with a broad spectrum of histological criteria
    - Only six trials required liver imaging at baseline
    - No consistency with respect to BMI, type 2 diabetes or lipid panel cut-off levels
        - ALT used as an inclusion criteria for 14 studies, with wide variability in cut-off levels
        - No consistent use of AST, bilirubin or platelets
    - Wide range of outcome measures also seen: many studies used resolution of steatohepatitis as primary outcome measure
- Some of the trends we saw were temporal: reflecting differences between earlier, completed trials and those that are ongoing
    - Some differences also can be explained by phase of trial, with proof of concept trials looking at biomarkers to explain mechanism of action
- Telephone interviews with study sponsors are being conducted to validate information obtained from ClinicalTrials.com and to obtain baseline measures

- We encourage industry sponsors to share baseline measure, when possible

Working Group Report (Andrew Muir and Joanne Imperial)

- This is a work in process; we hope others will find value in it
- The group is now going through the process of identifying an optimal set of baseline criteria to recommend for NASH clinical trials going forward
  - There will be an "essential" set and an "ideal set"
  - Additional work exploring tools to recommend to assess: dietary recall and nutrition; exercise and activity; quality of life; and alcohol consumption
  - A standardized list of concomitant medications (along with start/stop dates and dosage) is also being developed
    - We will also suggest concomitant medications that would constitute exclusion criteria
  - A standardized set of comorbidities would also be recommended
  - An "essential" set of biomarkers to recommend is also being developed
- Industry collaboration is critical to make this process work
- Discussion/Comments
  - Need to be careful not to create academic databases and stay focused on what we need for clinical trial drug development
  - Harmonization (standardization) offers several advantages:
    - Placebo arm data from trials standardizing their baseline data can be used as the foundation of a natural history cohort
    - Site capacity: if we are relatively consistent across trials with regard to eligibility criteria, it will include are capacity, across NASH studies, to conduct large studies; the sites will become much more functional and everyone will benefit
    - "the Coordinators' sniff test": when study coordinators have 20-30 trials at their site, each with a separate three hour screen, it will simplify and facilitate trials to have uniformity in eligibility criteria and baseline parameters collected
  - With regard to the development of biomarkers: if we work to define an essential group of biomarkers, we can validate those biomarkers by including them as essential baseline parameters to be followed in placebo arms
    - There may be industry concerns about sharing their proprietary information too broadly
  - The FDA has developed a guidance on tools for drug development
    - They encourage collaboration among sponsors
    - They, too, are concerned that with so many NASH-related trials in development, that there is the possibility of "running out of patients"
    - With standardized trial design, you can enroll multiple trials with one placebo arm, thereby saving patients
  - Everyone recognizes that heterogeneity is inevitable; no two people are going to design the same trial; even if two trials use the same protocol, their enrolled patient populations won't be identical.
    - We are trying to learn from a complicated situation in the midst of this heterogeneity—ways to reduce the unexplained variance
    - If we can accomplish that, then what is left will hopefully be the clearest, sharpest image of what a treatment does or does not accomplish

    - Our standardization efforts are trying to get to a nucleus of information that will allow us to determine whether Trial A's population is similar to or different from that of Trial B
        - We may find that a subset of Trial A patients are similar to a subset in Trial B;
        - In that way we might obtain natural history information which will enable trials to be done with smaller sets of (more similar) patients for shorter durations of time at less economic burden.
    - Most of these trials will require two biopsies; because of that the number of accrued patients will be small
        - For testing non-invasive diagnostics, we will need far larger numbers of patients
        - For the standardization of non-invasive biomarkers, the sample size may be 10-15-fold more than for the FDA [drug] registration studies
    - One commentator suggested that a letter of intent to pursue a collaborative effort among multiple industry/academic partners would be an important strategy to consider
    - Important to differentiate between the pharma and the diagnostic efforts
        - Validation of non-invasive biomarkers still relies on a gold standard; recommendation for a pre-IND meeting with regulators for companion diagnostics
        - Diagnostics trials similar to pharma trials and are very complex and need to demonstrate clinical utility
    - One of the advantages to the Forum's activities is the engagement with the regulatory agencies
        - it enables us to keep in line with regulatory definitions as we proceed
- From the pediatric perspective, a lot of issues are similar, but there are some special considerations
    - There is a mix of phenotypes in pediatric patients, just as in adults; it is very heterogeneous
        - There is a portal pattern of inflammation and fibrosis that has a very low prevalence in adults
        - That may constitute an earlier phase
    - There will need to be some standardization and some variables that are different for pediatrics
    - Some measurements that are acquired in adults directly from that person are acquired through a surrogate (often the parent) for pediatrics; so the set-up will be a little different
    - There are different disease categories for pediatrics
    - And we'll need to look at age-groups within the pediatric population
    - It is important to follow pediatric patients long-term; we don't know the 10-year, 15-year or 20-year natural history of the disease in the pediatric population
        - There are some cohort studies launching now
        - This may represent a golden opportunity for collaboration
- There will be different "buckets" of patients from different phases of studies
    - What a standardized baseline data set will look like for early phase 2 or proof of concept studies will likely be very different from that for a registration trial
- Data standardization with regard to testing of anti-fibrotic versus anti-inflammatory drugs
    - Different target population will be identified depending on mechanism of action
        - For anti-fibrotic drug, you will want to study patients with more advanced fibrosis

        - For an anti-inflammatory or immune modulatory drug, you will likely initially (e.g., Phase 2) choose a target population that doesn't have as much advanced disease
    - There may be differences in our endpoints depending on our target populations and according to phase of trial
    - From the regulatory perspective: Despite these differences, and keeping these two broad categories of drug development in mind, there are still good reasons to consider standardization in terms of trial design (depending on early or later phase trial), target population, endpoints and biomarkers
        - This exercise has validity despite all the complexities
        - Also for pediatrics, you cannot extrapolate data from adults to pediatric patients; placebo controlled safety and efficacy studies will have to be performed; there will not be waivers
- Our goal is to work together as a team to come up with the standardization plan
    - We will take into account phase of study, mechanism of action, etc. and bring forth recommendations
- Our hope is to improve and facilitate future study designs and potentiate a pooled placebo arm that can be used as a "universal" control group for future trials. We welcome your participation in our further efforts.

**Session #4a: Non-invasive Diagnostic Biomarkers**
**Overview:** Rohit Loomba
[Please refer to the accompanying slide set for further details: http://www.hivforum.org/storage/documents/2015/Liver_Forum/LF3/lf3%20final_non-invasive%20diagnostics_rloomba.pdf]

- A biomarker is a characteristic that is objectively measured and evaluated as an indication of normal biological process, pathogenic processes, or pharmacological responses to a therapeutic intervention.
    - There are composite and surrogate biomarkers. Surrogate biomarkers should meet the "Prince criteria". That is, the biomarker is elevated or decreased in disease state only, the biomarker gets 'worse' as the disease state gets 'worse' irrespective of the intervention, the biomarker improves as the disease state improves irrespective of the intervention, and predicts long-term risk of clinical outcome.
- Types of biomarkers include diagnostic, prognostic, predictive, and pharmacodynamics.
    - Diagnostic biomarkers help determine if a patient has NASH or not right now. It does not necessarily change with disease state.
    - Prognostic biomarkers, like HVPG, provide information on the likely outcome of the liver disease.
    - Predictive biomarkers change in response to therapy. They inform clinicians/researchers about the likely benefit from the treatment and who will likely benefit from treatment.
- The number of trials related to NASH/NAFLD is rapidly increasing.
- Natural history of NASH isn't well understood, but assuming linearity, it appears there is fibrosis progressions rate of 1 stage every 7 years. 20% of patients however will be fast fibrosis progressors.
    - 40-50% of people with NASH will develop fibrosis. 15-20% of those with fibrosis will develop cirrhosis, and once here, there is a 2-3% change per year of developing HCC as well as a 30-40% chance of liver mortality.

- Currently, liver biopsy is the only way to diagnose NASH. We need other methods.
- Key histologic predictors of mortality in NAFLD currently are presence of advanced fibrosis, presence of any fibrosis, and presence of NASH. Fibrosis has the highest prognostic value.
- When looking for new biomarkers, the first question should be biological plausibility. After you have determined that it is biologically plausible, then go on to study diagnostic accuracy, reliability and responsiveness.
    - To determine diagnostic accuracy, an AUROC (Area Under an ROC curve) will be helpful. For NASH, we want something above 0.9. There are lots of studies going on right now looking at the AUROC values for biomarkers for NASH.
    - Additionally, we want a test with high sensitivity and excellent negative predictive value (NPV) for clinicians. This screens and gets people in and then you can use a second test with high specificity. This two-step approach is what we do with HIV.
- Biomarkers can be looking at genomics, proteomics, lipidomics, metabolomics, and possible hybrid panels.
- Imaging techniques such as MR-based, Ultrasound, and CT is good for early phase trials and are another type of non-invasive diagnostic.
- Perhaps for early phase trials 1 and 2, primary endpoints should be more mechanism-based or could be imaging based. As clinical trials move on towards later stage 2 and 3 trials, the primary endpoints will change to harder endpoints that have more prognostic value.
    - For early phase trials, we want an efficient approach to quickly determine if the drug is engaging the intended target. If the drug is reaching its intended target, move on.
    - For later stage 2 and 3 trials, we will look at effectiveness. Ideally we are looking for drugs with high innovation and high effectiveness.
- For NAFLD initial assessment, we need non-invasive biomarkers to answer questions about the presence of NASH, NASH with fibrosis, NASH with advanced fibrosis, and risk of hepatic decompensation and mortality. This may require multiple biomarkers.
- For NAFLD prediction of treatment response, we want biomarkers that can predict the response – specifically we want biomarkers that predict the resolution of or improvement in NASH or improvement in one stage of fibrosis.
    - Currently, we can use MRI/MRS to measure improvement in steatosis.
        - There are benefits to both MRS and MRI, but MRI can give a picture of the whole liver, is available on routine scanners (GE, Siemens, Philips, etc.), doesn't require expertise of physicists, and the results are independent of field strength and are not effected by age, sex, BMI, or etiology of liver disease.
        - Make sure to co-localize when measuring fat in a study – look at the same spot in the liver before and after.
    - We need biopsy to measure resolution of or improvement in NASH.
    - We don't have reliable methods for measuring improvement in fibrosis.
        - Fibrosis has no molecular signature that can be detected by current imaging techniques. All imaging test measure fibrosis indirectly by looking at liver stiffness ("elasticity"). The rational is that collagen deposition that is associated with fibrosis imparts parenchymal rigidity on the liver.
        - There are many different methods now to measure liver fibrosis, including MR spectroscopy, MRI-PDFF, liver biopsy, and 2D MRE/3D MRE. 2D/3D

MRE is exciting because it is feasible, it analyzes a larger area of the liver giving a more comprehensive assessment, it allows us to co-localize, leading to higher precision and hopefully better efficiency in clinical trials. More work needs to be done to demonstrate this.
        - Caveats associated with imaging modalities include the fact that transient elastography or ARFI or other ultra-sound based tests are limited by obesity, ascites, acute inflammation and cirrhosis. MRE improves on these but is still limited by iron overload and acute inflammation. There is also a challenge in making imaging modalities that are accurate but also have high accessibility/ease of use.
    - We don't have reliable methods for measuring reduction in risk of hepatic decompensation and mortality.
- In summary, a biomarker needs to look for a cross-sectional association (diagnostic intent or screening a population). Validation should be done for biomarkers in large, multi-center cohorts. A change in biomarkers should accurately predict change in disease state over time, and biomarker levels should also predict treatment response and long-term prognosis.

**Session 4b: Moderated Panel Discussion: Opportunities for Collaboration Utilizing the Liver Forum**

**Moderators:** Scott Friedman and David Shapiro

**Panelists:** Celine Fournier, *Ecosens;* Herman Steen, *BiOrion Technologies BV;* Chris Leptak, *FDA/CDER;* Marc Hellerstein, *U.C. Berkeley/KineMed;* Greg Everson, *University of Colorado Denver;* Eric Lefevbre, *Tobira therapeutics, Inc.;* Steve Williams, *SomaLogic*

- Ultimately, our goal is to move past biopsy altogether. We want to have markers that can predict outcomes more reliably and predictably than biopsy.
- Biomarker collaboration: Regulatory agencies favor data sharing from placebo arms, from drug trials, or through a consortium type effort in order to identify the most promising biomarkers.
    - It is believed that pooled data will likely be more beneficial than each company focusing on a single biomarker.
- Three important areas of collaboration for biomarker use and development
    - One beneficial use of biomarkers is identifying what patients are at-risk for disease progression. We need to identify biomarkers that help us identify who will be a "progressor".
    - Additionally, using placebo-arm patients from a NASH clinical trial and comparing them to a healthy population of control could help identify NASH-related biomarkers and differences between this population and healthy controls.
    - Lastly, we need to validate the biomarkers we have for identify advanced stage (F4) cases of disease. We don't want to biopsy these individuals.
- What are good tools for Phase 2 trials that would allow a suitable biomarker to be used to make a decision about whether a drug would go forward to Phase 3?
    - We need biomarkers to show proof of mechanism which would be unique to each drug and typically one would have worked out earlier in development what those specific measurements would be to provide evidence for proof of mechanism. It is good to also use biomarkers to do surveillance for off-target effects of the drug. Finally, the biomarker evidence needed to determine whether or not to progress from Phase 2 to Phase 3 differs based on company. Small biotech companies have a lot to lose if they make a false termination decision. Larger companies

however have less to lose for a false termination and therefore may have a different biomarker threshold for progressing from Phase 2 to Phase 3.

- Liver elastography is correlated with liver fibrosis and Fibroscan is correlated with fat content, but neither of these is approved by the FDA. We need to work with the FDA to get these approved so they can be used for determining progression between phases of a trial.
- This perspective was offered from a small start-up with only one target and one technology:
  - Our use of biomarkers to determine progression from Phase 2 to Phase 3 is different than a bigger company.
  - That said, our therapeutic has a very specific target so we can use biomarkers to see if our drug is hitting that target.
- An alternative/more critical perspective is offered:
  - All biomarkers useful for other diseases (HIV, strep throat, Graves' disease, etc.) measure the cause or driving force of a disease.
  - The convincing step of a whether a biomarker is useful isn't regulatory – it's clinical. The best biomarker for NASH might be a blood-biomarker to measure the rate of fibrogenesis. We all believe that fibrosis predicts disease progression, so this makes a lot of sense to measure.
  - Instead of looking at as many biomarkers as we possibly can, we should specifically measure the biomarkers that make sense rationally and medically. We will need intervention trials, but the validation of successful biomarkers will be just as much clinical as trial-based.
- One company is currently measuring a CCR2 and CCR5 antagonist in a large study. This drug should decrease inflammation by reducing monocyte and macrophage infiltration, thereby hopefully decreasing fibrogenesis.
  - We are measuring a number of biomarkers that are specific to the drug's mode of action. We are looking at monocyte activation, macrophage activation, CCR2 and CCR5 ligands, and general systemic inflammatory markers.
  - We are also doing 2 post-treatment biopsies and will be comparing our biomarkers with the biopsies to determine if our biomarkers can predict the effects we see in the biopsy.
  - Liver biopsies have a low patient and physician acceptance, so we are trying to validate biomarkers to replace the biopsy eventually.
- How can we extend promising Phase 2 findings to Phase 3?
  - Based on our findings from the Phase 2 trials, we will decide which biomarkers to continue using in Phase 3.
  - We will look to see if any biomarkers have been predictive and specifically focus on bringing those into the Phase 3 trial.
  - Otherwise, it will still require biopsy and we will continue to compare the biomarkers with the biopsy results.
- Two additional points regarding diagnostics.
  - First, the liver is a functional organ and as our functional assays get better and better (they will), the functional assays should be looked at as a replacement to the diagnostic biopsy.
  - Second, we need to think about the stages of pathogenesis as well as the stages of resolution when we are looking at and measuring biomarkers.
- Scott Friedman: I'm going to reinforce 3 comments.

        - First, we've learned that successful antiviral trials show the default state of the liver is to regenerate and to block fibrosis. It stands to reason that if we attenuate the drivers of disease, the liver will help us along the way.
        - Second, when thinking about which biomarkers to measure we really need to be focusing on biological plausibility, whether it's related to pathogenesis of inflammation, fibrosis and/or function.
        - Finally, we're struggling because we haven't had a major success, but I believe when we get closer to major success we'll know it.
- Veronica Miller: In conclusion, when we look at successes like HIV, what really got the viral load validated as a surrogate endpoint was collaboration amongst all the companies that had a clinical endpoints trial and who were all measuring viral load. Companies had a standardized analysis plan. Although they didn't pool data, they all collaborated. I see a couple of ways forward.
    - First, we can make a new working group that can focus on developing a more standardized approach to how to bring in certain biomarkers in a systematic and logical way into some of the studies.
    - Second, we need to take a big step in thinking about what it means if we actually start pooling the data and looking at the bio-repositories and other data we have. This type of collaboration will take a lot of effort and will need infrastructure to do this.
- It's important to understand we are trying to get companies to look at the same problems in the same way. We need to standardize the data that is collected but also the protocols that generate the data. This helps us standardize data across studies and determine is the biomarker good or not or is it the assay that is the problem?
- So what will this actually look like if it's successful?
- The FDA will likely have a panel of biomarkers that we can say if you have a certain mechanism of drug, this is maybe a panel we would suggest. This is going to have to be worked out in between the biomarker companies and the drug companies to collaborate, but I think we can help that process of collaboration within this Forum. NASH itself is tricky because it is typically asymptomatic with a very long natural history. It's hard to know when we have something great because patients don't typically feel bad to begin with, and it takes years to see the clinical benefit endpoints. Because of this, NASH is a very difficult disease.
- Comments from audience:
    - Diagnostic and therapeutic companies could collaborate so that some companies that are already doing biopsies on patients to test a drug could collaborate with diagnostic companies to test the new diagnostics. This could help validate diagnostics for a lower cost and could add to the data of the therapeutic efficacy trial.
    - Would it be possible to initiate a larger, sort of collaborative effort to monitor disease progression biomarkers across populations similar to what the Michael J. Fox Foundation is doing with the Parkinson's Progression Markers Initiative.
- Conclusion:
    - Are there academics and clinicians in the room who would be interested in creating a baseline disease and biomarkers project to submit and pool data (tissue, blood, etc.)? [Lots of people raised hands]
    - Are there people in the diagnostics community who are interested in participating in collaborations with therapeutic companies? [Lots of people raised hands]
    - Are there people in therapeutics who are willing to share some data and possibly send blood/tissue samples for pooled date? [People raised hands]

- There seems to be general consensus and willingness to collaborate, so let's move forward from here!

**Session 5:** Announcements and Wrap-Up

- **EPoS: Elucidating Pathways of Steatohepatitis – The European NAFLD Registry** (Quentin Anstee) [Please refer to slide set for further details: http://www.hivforum.org/storage/documents/2015/Liver_Forum/LF3/lf3%20final_epos%20eu_qanstee.pdf ]
  - EPoS is an EU Horizon 2020-funded program. It's a large, multi-center program with ten centers across Europe participating. It is a direct successor of the FLIP program that Vlad Ratziu coordinated. EPoS is an EU-funded project, but it is open to facilitating work with other centers.
  - The basic discovery science elements of the EPoS program are that fatty liver disease is based on the sum of our genetic, epigenetic, and environmental factors. If we study all of these in a well-defined patient cohort we can get a global assessment of what is actually driving the pathophysiology of this condition.
  - EPoS therefore takes a large, well-characterized, biopsy-proven NAFLD cohort and applies multiple "omics technologies" and then uses a large systems biology approach to interrogate the data and hopefully draw additional knowledge.
  - 2 areas of the EPoS program are most relevant to us – Work Package 1 (WP 1) focusing on patient cohorts and Work Package 9 (WP 9) focusing on biomarker discovery.
    - WP 1 has established the European NAFLD Registry (with additional funding from EASL) in order to supply sufficient tissue and samples to support the EPoS program. WP 1 is actively building on the FLIP cohort and is recruiting individuals from a number of additional centers across Europe to add information to the European NAFLD Registry. There are very clear entry requirements and patient protocol. Information is collected on: anthropometrics, medical history, drug history, routine chemistry, diet and lifestyle, histopathology of liver samples, serum, liver tissue, urine and feces. All of the data will be entered into an integrative omics analysis. The cohort is currently over 1,100 cases. Additionally, this cohort will be followed up longitudinally with annual re-data collection and serum sample collection for biomarker use.
    - WP 9 is the biomarker discovery work package and is looking at current serum fibrosis markers to help validate them for clinical decision-making. It is hoped that a combination of serum markers with elastography may be a useful way of leveraging the high negative predictive value of some of these tests in helping with clinic decision-making. WP 9 is also looking for more direct markers that are more sensitive and specific surrogates for fibrosis. WP 9 will continue to evaluate novel biomarkers that are coming through the research pipeline.
- **IOM Report** (Arun Sanyal)
  - Introduction: Today we've discussed a multitude of phenotypes that the disease process can take. The intermediate phenotypes are not completely defined yet, but this is an iterative process. As we move forward and continue to engage, hopefully our understanding will continue to mature. Furthermore, at the end of the day we have to bring it back to regulatory bodies and see how we can identify the principle populations of interest. Ultimately, even when we get things through the regulatory agencies and approved, we need to think about access to care,

awareness, and ultimately third party payers for drugs. We have to get through all these steps.

- In the US, perhaps the most influential group for impacting health policy and access to care is the Institute of Medicine. We saw with Hepatitis C that so much of the change on the ground with Hepatitis C resulted from an IOM report about 6 years ago. Therefore, it is a very exciting opportunity for us to engage with the IOM to potentially conduct a study and create a report that would highlight the importance of the disease, identify where there are major gaps in terms of knowledge, awareness, or access to care, and to emphasize the significance of the public health problem. This could help drive policy decisions to funnel resources to those gaps.
- In order to conduct this study, the IOM needs the financial resources to fund the study. It is a 15-month process from when the IOM sits down to when the report is issued. We need to raise the $1.2 million still needed for the IOM to begin the study. The sooner the IOM can begin; the sooner things can change on the ground in the field of NAFLD. We are asking each of you to return to your companies and see if you can contribute funds to this endeavor. We will also be applying for federal agency funding as well so hopefully this could truly be a public-private endeavor.

- Thanks are offered to all participants and the meeting is adjourned for the networking reception.