New Working Group:
Radiology Liver Disease (RLD) Program

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Disclosures

Consultation:	Alimentiv, Arrowhead, AutonomUS, Glympse, Kowa, Median, Novo Nordisk
Lab service agreements:	Alexion, AstraZeneca, Bristol-Myers Squibb, Celgene, Enanta, Galmed, Genzyme, Gilead, Guerbet, Intercept, Ionis, Janssen, NuSirt, Organovo, Pfizer, Roche, Sanofi, Shire, Synageva, Takeda
Grants:	Livivos
Stockholder:	Pfizer
Co-founder:	Quantix Bio

Need for a Radiology Liver Disease (RLD) Program

Current similar efforts:

Radiology Committee, NIH NASH-CRN
Radiology Committee, NIH Liver Cirrhosis Network (LCN)
LITMUS and NIMBLE Studies
FDA Biomarker Qualification Program (BQP)
Quantitative Imaging Biomarker Alliance (QIBA) – many groups, all ending soon

Major gaps in these efforts:

Require NIH, FDA, or professional society funding/support – thus, all self-limited
Agendas are (necessarily) narrow
None provide egalitarian inclusion of all stakeholders

The Liver Forum RLD Program will help bridge and address these gaps.

Overview

Mission Statement:	To provide broad, relevant, and diverse Radiology expertise to the Liver Forum
Vision Statement:	To incorporate RLD Program expert consensus opinion and guidance on implementation and interpretation of liver imaging in drug development clinical trials, and in future patient care
Major objective:	To facilitate inclusion of radiologic imaging methodology in the study of liver disease, ensuring stakeholder alignment and collaboration to advance drug development clinical trials
Immediate goals:	• Invite ***broad, relevant, diverse*** participation • Form **Working Groups**; appoint **Executive Committee** • In consensus, decide on an agenda • **Report back to Liver Forum at LF16 (Q2 2024)**
Invitation to participate:	• Liver Forum Events and emails • Key individuals who do not currently participate in the Liver Forum

Broad Additional Aims

1. Plan and coordinate ***long-term strategy:***
   - to ***assess and validate promising quantitative imaging biomarkers*** for drug development, such as through the FDA Biomarker Qualification Program (BQP) and/or through AI methods, and
   - ***later for clinical care*** in collaboration with professional society consensus groups
2. Liase with new ***SLD Working Group*** to ensure uniform terminology adoption
3. Determine ***minimum requirements for regulatory biomarker validation*** through an inclusive approach incorporating input from industry, academia, and regulatory stakeholders
4. Identify ***knowledge gaps, anticipated potential barriers, and possible solutions*** to achieving these aims
5. Provide ***standardization***, and ***radiologic guidance***
6. ***Liase with industry*** to use completed clinical trial data to advance biomarker science.

RLD Tasks and Working Groups

Standardization – low level fruit

and

Three initial proposed Working Groups

- Diagnostic Enrichment – Opportunities
- Treatment Response – Challenges and Solutions
- Pediatric

Standardization

- Most SLD drug development clinical trials require **central imaging management:**
  - *Qualification*
  - *Acquisition*
  - *QC*
  - *Analysis*

  Central management **expensive**, and **siloed** within individual clinical trials and thus duplicative, but better than site-based management.
- Site-based management improvement: ↓ study costs, ↑ data reliability in clinical trials, and later will be necessary for **patient care** following treatment drug approval

Liver Forum RLD Program well poised to improve site- and centrally-based imaging biomarker management across clinical trials

Diagnostic Enrichment - Opportunities

- **LITMUS** and **NIMBLE trials**, and **several FDA BMQ Applications** likely will provide sound, tested data to permit decisions based on extrapolations of that data to inform clinical trial biomarker selection and study design
- **The Liver Forum RLD Program should be well poised to**:
  - provide additional multi-disciplinary input on how those extrapolations can be accomplished, and
  - provide additional insight on what new studies might be helpful, and what new FDA BMQ applications might be needed.

Treatment Response – Challenges and Solutions

Literature review: At LF14, PubMed search for “NASH + treatment response” yielded 107 papers; 10 discussed; now yielded 119 papers, but no new papers remained to review.

Problems:

- Limited precision of ***non-invasive imaging*** *and* ***reference histologic biomarkers*** *for SLD*
- No clear pathway to ***outcome-based non-invasive biomarkers*** of treatment response

Major challenges:

- Variability of change is doubly affected – ***at baseline***, and ***at end-of-treatment***
- Accuracy of non-invasive biomarkers can be no better than that of reference histology
- Limitations magnified when biomarkers used to provide individualized patient care

Tentative solutions:

- Improve histologic precision by ***acquiring two biopsies*** (not feasible)
- Improve histologic precision by ***refining current histologic analysis***
- Improve histologic precision by ***use of AI***
- Improve non-invasive SLD imaging biomarker precision by improving QC, improving routine analysis, and developing AI analysis

Pediatric Considerations

- Pediatric NAFLD (old terminology) has a **prevalence** in USA of 5-10%[1,2]
- Up to **16 million children in USA eligible for NAFLD screening** as per new pediatric guidelines[3-6]
- Children with NAFLD have **30x higher risk of T2DM** than children with obesity alone[7,8]
- Pediatric gastroenterologists **manage children with NAFLD more aggressively** than they do children with obesity alone.
- Thus, unified radiologic approach needed for pediatric, as well as for adult clinical trials.

The proposed Pediatric Working Group (as part of the Liver Forum RLD Program) will help provide guidance to pediatric SLD clinical trials.

References for this slide:

1. Sahota et al, *Pediatrics*, **2020**; 146:e20200771 (PMID: 33214329)
2. Schwimmer et al, *Pediatrics*, **2006**;118:1388-1393 (PMID: 17015527)
3. Vos et al, *J Pediatr Gastroenterol Nutr*, **2017**; 64:319-334 (PMID: 28107283)
4. Mischel et al, *J Pediatr Gastroenterol Nutr*, **2023**; 77:103-109 (PMID: 37084344)
5. Hu et al, *JAMA Pediatr*, **2022**; 176:1037-1039 (PMID: 35877133)
6. U.S. Census Bureau, **2020**; https://www.census.gov/data/tables/2020/demo/age-and-sex/2020-age-sex-composition.html
7. Simon et al, *Gut*, **2021**; 70:1375-1382 (PMID: 33037056)
8. Newton et al, *Clin Gastroenterol Hepatol*, **2023**; 21:1261-1270 (PMID: 35709934)

Summary and Future Plans

- SLD Clinical Trial needs would benefit from Liver Forum Radiology involvement.
- Liver Forum Radiology Liver Disease (RLD) Program will address many of those needs.
- Liaison with New SLD Working Group will ensure unform adoption of the new terminology.
- We are inviting interested stakeholders to take part in the Liver Forum RLD Program.
- We expect to have assembled interested participants, to have met, and to have decided on a preliminary agenda by Q2 2024, and plan to report progress back to the Liver Forum by that time.

Thank you

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