Berkeley School of Public Health

Forum for Collaborative HIV Research

Updates from Liver Forum and IOM Initiative

Paris NASH Symposium

Institute Pasteur

Veronica Miller, PhD

School of Public Health, UC Berkeley

July 1, 2016

Disclosures

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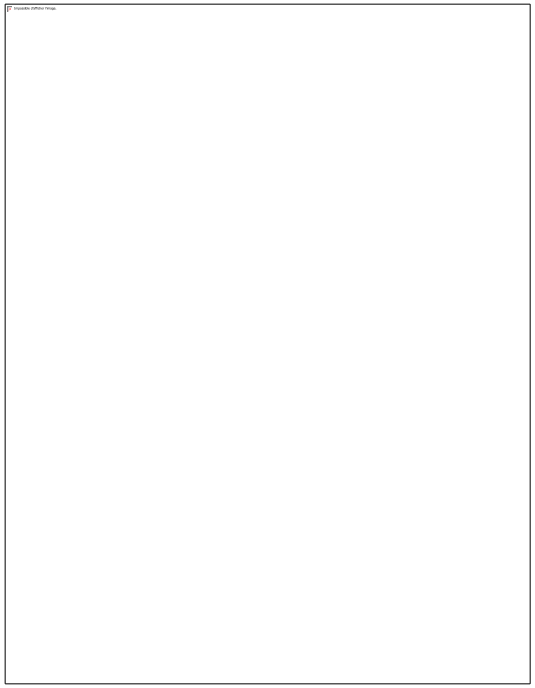
Over the last two years, the Forum has received unrestricted educational or research contributions from:

Abbot; Abbvie; Achilion; Akarna Therapeutics; Alere; Astellas; Astra-Zeneca; Biogen; BioRAD; Boeheringer Ingelheim; Bristol-Myers Squib; Cell Medica; Chimerix; Cocrystal Pharma, Inc.; Covance; DDL Diagnostics; DeuteRx; DiaPharma; DS Biopharma; Echosens; Exalenz; Fibrogen; Fractyl; Galectin Therapeutics; Genentech; Genfit; Gilead Sciences; GlaxoSmithKline; ICON; Illumina; Immuron; Intercept; Ironwood Pharmaceuticals; Janssen; Kaiser Permanente; LabCorp; Lilly; Madrigal Pharmaceuticals; Mallinckrodt Pharmaceuticals; MediciNova; Medivir; Merck Laboratories; Microbiotix; Monogram; Mylan; NGM Biopharmaceuticals; Nimbus Therapeutics; Nitto Denko Technical Corp; Novartis; Novo Nordisk Inc.; Nusirt; Orasure; OWL Metabolomics; Pacific Biosciences; Perspectum Diagnostics; Pfizer; PPD Inc.; Presidio; Qiagen; Quest; Quintiles; Raptor Pharmaceuticals; Resonance Health; Roche Molecular Systems; Roivant Sciences; RuiYi; Salix (Valeant); SeraCare; Schinazi Family Foundation; Shire; Somalogic; Takeda; Tobira; ViiV Healthcare; VLVBio; Zafgen and Zealand Pharma.

Full Disclosure



Happy Canada Day!

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Improving the Health of the Public

- Drug Development(what):
  - Process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery
- Regulatory Science (how):
  - Science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of all FDA regulated products
- Public Health Goal (why):
  - Maximizing benefit of treatment while decreasing safety risk

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Path to Improved Access to Drugs and Diagnostics

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1. Discover and develop diagnostics and therapeutics (R&D)
2. Develop regulatory path, review and approve diagnostics and therapeutics
3. Bring to Market
4. Implement
   - Screening, diagnosis, treatment
   - Treatment guidelines
   - Reimbursements

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From Yesterday

- NASH
  - We don't know how to find it
  - We don't know how to define it
  - We can't diagnose it
  - We don't have an indication for treatment
- We don't even know how to name it
- BUT –
  - We know it's an unmanageably huge public health problem for children, adolescents and adults across the world

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NASH Challenge to Industry

- Development of new therapeutics in absence of
  - Realistic and pragmatic regulatory path
  - Validated and accepted biomarkers
    - Diagnostic, prognostic, predictive and surrogate endpoint
  - Precise definitions of disease stages/progression
- Requires co-evolution of diagnostics and therapeutics

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Challenge to Regulators

- Develop regulatory guidance in an area where none existed
- Safeguard the health of the public while fostering innovation

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Challenge to NASH Community

- Likely need for combination treatment
  - When is it safe to combine?
- Long-term follow up vs. placebo
  - Ethics? Feasibility?
- Research in pediatrics
  - When is it appropriate to test new drugs in children and adolescents?

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CLINICAL PHARMACOLOGY & THERAPEUTICS

nature publishing group

Open

STATE OF THE ART

Accelerated Access to Innovative Medicines for Patients in Need

LG Baird[1], R Banken[2], H-G Eichler[3], FB Kristensen[4], DK Lee[5], JCW Lim[6], R Lim[5], C Longson[7], E Pezalla[8], T Salmonson[9], D Samaha[2], S Tunis[10], J Woodcock[11] and G Hirsch[1]

- Current “siloed” system increases development cost, time and risk
- Inefficient use of accelerated access programs
- FDASIA Legislation (2012): apply principles more broadly
- Increased cross-jurisdictional and cross-functional interaction
- Increased engagement of all stakeholders

THE KEYSTONE NATIONAL POLICY DIALOGUE ON ESTABLISHMENT OF STUDIES TO OPTIMIZE MEDICAL MANAGEMENT OF HIV INFECTION

FINAL REPORT
AUGUST 2, 1996

EXECUTIVE SUMMARY: Significant government and private sector efforts in basic and applied research have led to an explosion of *new scientific knowledge that could transform the battle against HIV infection.* There are new insights into the pathogenesis of HIV infection, greatly improved monitoring tools, and increasingly effective antiretroviral therapies that more profoundly suppress the epidemic the opportunity may exist to from a relentlessly progressive disease to a dition, reduce transmissibility of the virus, mic itself. In order to take advantage of this

...

TECHNOLOG

Groups Unite on New AIDS Drug Therapies

By MICHAEL WALDHOLZ
Staff Reporter of THE WALL STREET JOURNAL

Representatives from 40 public and private organizations have forged an unprecedented alliance to press for answers to the many vexing questions surrounding the new combination-drug therapies that are showing early yet profound success against the virus that causes AIDS.

The coalition will help organize research to determine which of the new drug "cocktails" work best, when should therapy be initiated, and what steps can be taken to avoid the development of widespread drug resistance that could devastate the new therapies' effectiveness.

"The new treatments have a degree of complexity not faced before in AIDS," said Linda Distlerath, a Merck & Co. official who is a member of the organization. She added that the group will try to "facilitate and coordinate" numerous clinical trials in the next few years.

The coalition includes officials from the White House and several government-health agencies, several pharmaceutical companies, research-medical centers, private and government health insurers, and patient-advocacy groups. The representatives came together earlier this year after Vice President Al Gore held an initial meeting with many of the participating organizations.

"This is precisely the kind of dialogue patient-treatment advocates have been asking for years," said David Barr of the Gay Men's Health Crisis, New York. "One thing that's been very frustrating to us over the years is the lack of coordination

and conversation among
Under the auspices
Center, a Colorado non
officials met privately fiv
ington. On Friday, the gr
President Gore and an
nership, to be called the
rative HIV Research.
In recent months, seve
that combining several
drugs can suppress HIV,
more potently than any t
The new drugs, called pr
have been available since
But already there is evi
used with older drugs, s

THE WALL STREET JOURNAL MONDAY, AUGUST 5, 1996 B3

Y & HEALTH

skipping the regimen can allow the virus to re-emerge, perhaps in a form that is resistant to all existing medicines.

Moreover, doctors and patients are confused as to how best to combine the medicines. Constance Benson, a research physician at Rush Medical College, Chicago, said she and her colleagues are uncertain because the new drugs were approved quickly, following only limited safety and effectiveness trials.

"We need a more rational way to answer the questions our patients ask us," Dr. Benson said. "They want to know when to go on the therapy, how long they need to take the drugs, which drugs to start with, when can they stop."

Initially, the Forum will encourage several large-scale drug trials to test which of various treatment strategies works best. One already under development will involve several thousand patients and last three to five years. "[The trials] will require an enormous amount of financial resources, the cooperation of many drug companies" and many medical centers and other groups, such as Veterans Administration hospitals, health-maintenance organizations, and state and federal-government insurers, such as Medicaid, Dr. Benson said.

Nordson's New Facility in India

WESTLAKE, Ohio—Nordson Corp. said it established a facility in India, Nordson India Pvt. Ltd., to market materials-applications technologies, increasing the company's world-wide direct operations to 31.

DIMENSION X INC.

Microsoft Corp. has agreed to license three-dimensional graphics technology from a little-known San Francisco start-up, **Dimension X** Inc., a closely held company with 35 employees, said Microsoft will use its software technology in future versions of Internet Explorer, Microsoft's software for browsing the Internet's multimedia World Wide Web. The start-up's products include Liquid Reality, a tool for creating and viewing Web sites that have a 3-D appearance. Microsoft said it will use Dimension X software based on industry specifications called VRML 2.0, and combine it with a technology called ActiveX that Microsoft is promoting as a standard way to create moving images inside a Web page. Terms weren't disclosed.

Accelerating Access to Better and Safer Drugs for All

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- Forum Model:
  - Stakeholder collaborative model
    - Process of dialogue and deliberation
    - Government, industry, academia, community
    - HIV
    - HCV, CMV/transplant recipients, HBV
  - Identify gaps and barriers
    - Recommend consensus, solutions, fund/engage in new research path

Clinical research & post-marketing commitments

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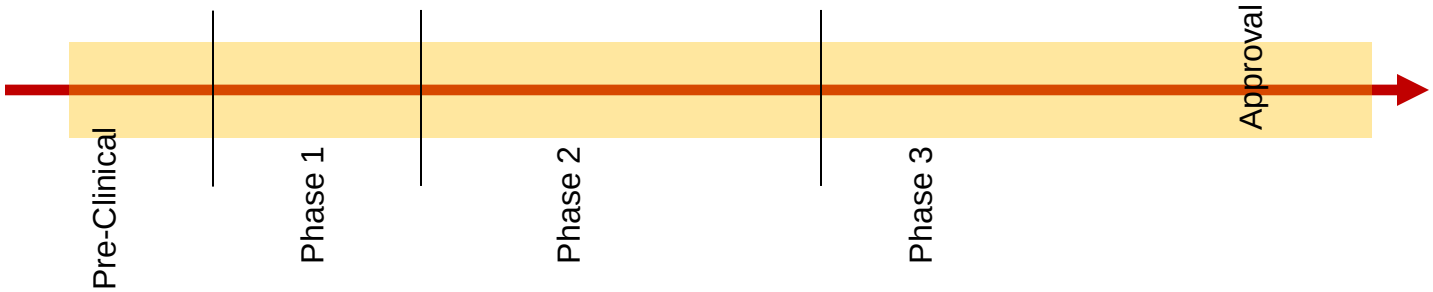

- Expected costs and time to registration?
  - Uncertainty regarding acceptability of study designs
  - Interagency discordance on trial designs & acceptable endpoints
  - Post-marketing safety requirements
  - Inefficient investigator and patient recruitment

Regulatory Process

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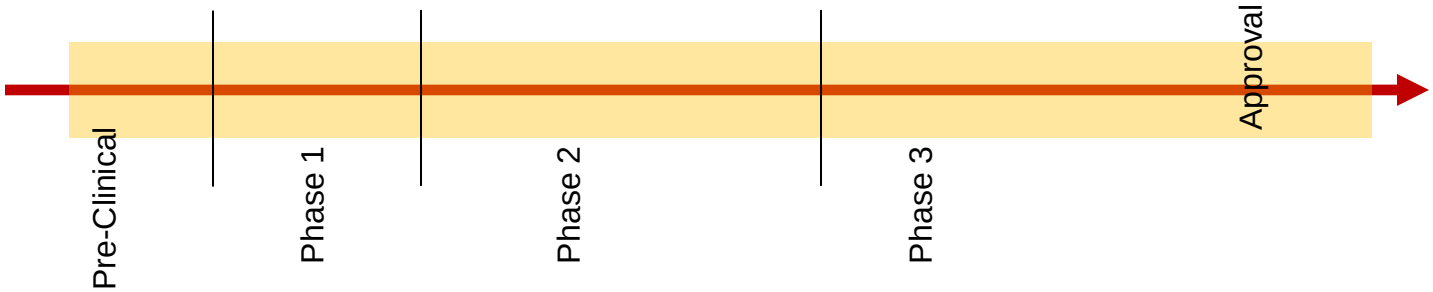

- Sponsor ↔ Agency
  - Single sponsor
  - Single agency
  - Confidential proceedings
- Advantages of Forum model
  - Involvement of *all* concerned stakeholders
  - Cross-Atlantic regulatory perspectives
  - Cross-Atlantic academic and patient/community perspective

Organizational Model

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- Informal yet structured
  - Allow organic growth
  - Lack of bureocracy
- “Non-player ecosystem orchestrator”
- “Multi-stakeholder partnerships that enables adaptive management”

- Experts participate as individual experts, not officially representing their respective organizations
- Not for attribution

Key Characteristics

- “Information Democracy”
- Non-competitive, safe environment
- Independent
- Co-ownership
- Synergy vs. duplication
- Transparency

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Impact on Drug Development

- Increase
  - Clarity
  - Efficiency
  - Collaboration
  - Innovation
- Decrease
  - Uncertainty
  - Redundancy
  - Development time
  - Risk

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Win-Win

- Accelerate drug development not by lowering standards of evidence, but by increasing efficiency through collaboration

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The Liver Forum:
Facilitating Drug Development For NASH

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- Independent and neutral venue for evolving consensus on drug development and regulatory issues
  - *Increase* clarity, efficiency, innovation
  - *Decrease* uncertainty, redundancy, time, risk
- Safe space
- Collaboration
- Win-Win

<u>One table</u>:

- Regulators
  - FDA
  - EMA
- Academic
  - US
  - Europe
- Societies
  - AASLD
  - EASL
- Industry
  - Pharma, biotech, diagnostic
- Patients

NASH Drug Development

- Phase 2b trials
  - 2014: 4
  - 2016: >50

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Precipitating Event

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

SPECIAL ARTICLE

Challenges and Opportunities in Drug and Biomarker Development for Nonalcoholic Steatohepatitis: Findings and Recommendations From an American Association for the Study of Liver Diseases–U.S. Food and Drug Administration Joint Workshop

Arun J. Sanyal,[1] Scott L. Friedman,[2] Arthur J. McCullough,[3] and Lara Dimick-Santos[4]

- Need for ongoing dialogue and interaction
- One-off efforts raise issues but do not resolve them
- Apply HIV Forum model

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Liver Forum Timeline

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2013:

- AASLD-FDA joint workshop

Recruit AASLD and EASL leadership

- Q4 2013/Q1 2014

Recruit FDA and EMA participation

- Q4 2013/Q1 2014

Develop concept note

- Q1 2014

Establish Steering Committee

- Q1/Q2 2014

LF1: AASLD/ Boston, 2014
LF2: EASL/Vienna, 2015
LF3: AASLD/San Francisco, 2015
LF4: EASL/Barcelona, 2016
LF5: Boston, 2016

Liver Forum Steering Committee

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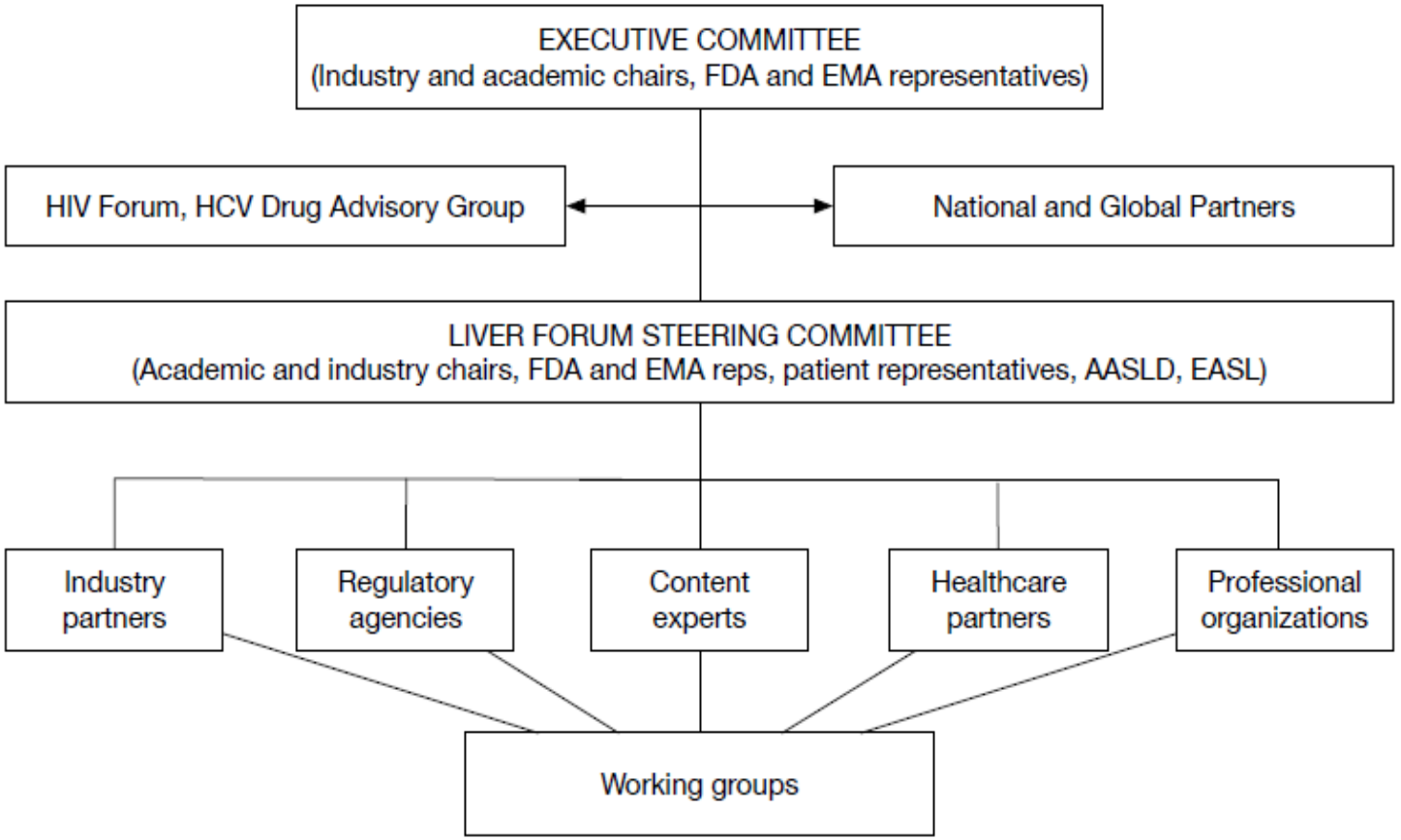
- Co-chairs
  - Gary Burgess, *Conatus*
  - Arun Sanyal, *VCU*
- FDA
  - Lara Dimick, *CDER/DGIEP*
  - Ruby Mehta, *CDER/DGIEP*
  - Chris Leptak, *CDER/OND*
- EMA
  - Elmer Schabel, *BfArM*
- Carol Brosgart, *UCSF*
- Laurent Castera, *Hôpital Beaujon*
- Stephen Harrison, *Brooke Army Med Center*
- Tom Karlsen, *Norway/EASL*
- Scott Friedman, *Mount Sinai*
- Joel Lavine, *Columbia*
- Veronica Miller, *HIV Forum*
- Massimo Pinzani, *UCL*
- Detlef Schuppan, *Mainz Uni Med Center/BIDMC*
- Helena Brett-Smith, *BMS*
- David Shapiro, *Intercept*
- Donna Cryer, *Global Liver Institute/Patient Rep*
- William Baldyga, *Patient Rep*

STRUCTURE OF THE LIVER FORUM



Strategy

- Collaborative dialogue and deliberation on urgent gaps
- Share leadership among academic and industry experts
- Build trust
- Allow consensus to evolve
  - Always science based
  - Don't force it if the science does not back it
  - Identify knowledge gaps and mechanisms to address these gaps
- Build more trust
- Tackle more challenging issues

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Initial Key Questions

- Which patients are most at risk for progression?
  - Early stages (NAFL)
  - Later stages (NASH, NASH + Cirrhosis)
- Which patients are most likely to respond to an intervention?
- How do we identify them?
  - Adults
  - Adolescents, pediatrics
- How do we know when the intervention has worked?

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Pragmatic Goals

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- Work towards acceptance of biomarkers for
  - Defining disease stage
    - Diagnostic and prognostic
    - Patient selection; inclusion/exclusion criteria
  - Intervention
    - Predictive, pharmacodynamic and endpoint surrogate markers
- Facilitate the establishment of a natural history cohort
  - Placebo arm data, other data sources

Urgent/Immediate Gaps

- Address through dialogue and deliberation:
  - Lack of consensus on disease definition
  - Lack of standardization of baseline parameters

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Working Groups

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- Disease definitions
  - Across NAFLD and fibrotic progressions
- Standardization of baseline data
- Challenges in pediatric drug development

- Biomarker validation
- Placebo-armed based natural history cohort

Outcomes

- Recruitment of key US and European players
- Cross-talk between regulatory agencies
  - “informal harmonization”
- Key recommendations
  - Standardized assessment of baseline parameters
  - Disease/stage definitions
  - Recommendations for pediatric development programs

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Outputs (Q1-Q2-2016)

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3 Consensus manuscripts

- Disease definitions suitable for RCT's/regulatory context
  - Living document
    - Start with currently available data
    - Integrate new non-invasive dx as data becomes available
- Recommendations for standardized baseline assessments
  - Facilitate cross-study comparisons
  - Natural history cohort
- Pediatric perspective/special issues in drug development
  - Set stage for pediatric drug development

Opportunities to be Tapped

- Innovation in clinical trial design
- Innovation in data analytics
- Translation of model to
  - Alcoholic steatohepatitis
  - DILI in context of underlying liver disease

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Path to Improved Public Health

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1. Discover and develop diagnostics and therapeutics (R&D)
2. Develop regulatory path, review and approve diagnostics and therapeutics
3. Market
4. **Implement: POLICY MAKERS**
   - **Screening, diagnosis, treatment**
   - **Treatment guidelines**
   - **Reimbursements**

NASH: Invisibility

- Individual
  - Symptom free until too late
  - Lack of awareness
- Population level
  - Surveillance
  - Natural history data
    - Adults
    - Children
    - Transition from childhood-adolescence-adulthood

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Invisibility

- Clinical
  - No mandate for screening
    - “be vigilant”
  - Lack of diagnosis
    - Liver biopsy dependent

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Invisibility

- Public Health
  - Focus on obesity, diabetes, cardiovascular
  - Focus (and success!) on viral hepatitis
  - Lack of awareness of the role of the liver
  - Natural history, surveillance
  - No practice guidance to screen for NAFLD or NASH

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Invisibility

- Societal
  - Stigma
  - “Life Style”

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Invisibility

- Policy Level
  - Lacking leadership at federal level
  - Education
  - Prevention

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http://www.cdc.gov/cancer/liver/index.htm

Liver Cancer

Cancer is a disease in which cells in the body grow out of control. When cancer starts in the liver, it is called *liver cancer.* Each year in the United States, about 20,000 men and 8,000 women get liver cancer, and about 16,000 men and 7,000 women die from the disease. The percentage of Americans who get liver cancer has been rising slowly for several decades.

To lower your risk for liver cancer, get vaccinated against Hepatitis B, get tested for Hepatitis C, and avoid drinking too much alcohol.

Invisibility

- Governmental
  - Who “owns” the liver?
    - Viral hepatitis?
    - Chronic diseases?
    - Cancer?

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IOM Study

- Awareness
- Policy
- Education
- Prevention
- Treatment

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IOM: HCV + HBV

HEPATITIS AND LIVER CANCER

A National Strategy for Prevention and Control of Hepatitis B and C

Heather M. Colvin and Abigail E. Mitchell, *Editors*

Committee on the Prevention and Control of Viral Hepatitis Infections

Board on Population Health and Public Health Practice

U.S. Department of Health & Human Services

COMBATING THE SILENT EPIDEMIC of VIRAL HEPATITIS

Action Plan for the Prevention, Care & Treatment of Viral Hepatitis

Last Word

- All the innovation in the world will not benefit patients if the will to implement (screen, diagnose, treat, and reimburse) is lacking

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EASL European Association for the Study of the Liver

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