data over 1 min. We also used intravital arbitrary region image correlation spectroscopy (IVARICS)—an orthogonal approach which is based on correlations between pixels, with a 2–32-μs dwell time per pixel. The limits of detection for flow velocities are even lower for IVARICS. Due to this, we believe that, despite the challenging dimensions of the canaliculus, the sensitivity of our techniques surmounts this challenge. It was equally surprising to us that even with this unparalleled sensitivity, we did not find evidence of flow within the canaliculi under basal and stimulated conditions.

We have discussed to some extent the transcellular and paracellular pathways through which ions may enter the bile canalicular network. Both aquaporins and claudin are bidirectional permeability enhancers, and their presence does not necessarily imply a net movement of water in any direction. A net movement of water would require a chemical potential, which has been postulated to be derived from the osmotic activity of ions secreted into the bile.

However, because we found no evidence of such water movement through the canalicular network, we proposed an alternative model that explains all extant and recent findings. In this model, choleresis occurs due to stimulation of cholangiocytes through components in the bile or blood. Some of these components, such as ATP, histamine, glutathione, and bile salts, are known choleretic agents, exerting their effect through stimulation of receptors on the cholangiocyte membrane or on cilia. The secretion of these "endogenous" choleretics is influenced by a variety of transporter activities and intracellular and paracrine signaling pathways.

For example, gadolinium chelates such as gadobenate dimeglumine (BOPTA) are known to cause a release of histamine,[1] as well as to enhance glutathione levels.[2] Such effects on endogenous choleretics could lead to increased bile flow that is only indirectly correlated to the concentrations of BOPTA in hepatocytes. While the exact mechanism for the BOPTA-induced choleretic effect remains unknown, hints of an indirect effect are seen from the related compound Diethylenetriamine-pentaacetate (DPTA) Gd-chelate, which has a lower osmotic coefficient, accumulates to similar levels in hepatocytes, but causes 250% more bile flow than BOPTA.[3]

CONFLICT OF INTEREST

Nothing to report.

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Letter to the editor: Importance of universal screening for chronic hepatitis B infection in adults in the United States

To the editor,

We write in support of universal screening of adults for chronic hepatitis B infection in the United States, in response to the article "Optimizing Hepatitis B Virus Screening in the United States Using a Simple Demographics-Based Model."[1] The authors stated that in the United States, universal screening would not likely be cost-effective. However, no recently published cost-effectiveness studies support this. In fact, a recently published study concluded that "universal HBsAg screening of adults in the US general population is not only cost-effective but would save an estimated $596 million and prevent an additional 23,000 deaths … compared with current risk-based and country of origin screening recommendations."[2]

Current risk-based screening strategies have failed, and as a result, only a small proportion of people living with

hepatitis B in the United States are identified and in care and treatment.[3] Although country of birth (COB) could assist with identifying additional infections, this information is not consistently collected. Many of those on the front line of screening for hepatitis B are smaller primary care practices that are not equipped to do so. Additionally, collecting COB can be sensitive for both health care staff and patients,[4] and there is considerable concern about possible discrimination associated with such questions.[5] This is especially true now with concerns of stigma and harassment of immigrants and anti-Asian racism.

Although machine learning might be able to identify high-risk people, there are significant challenges to its widespread implementation. Overall, universal screening followed by linkage to care is the single best way to ensure that people living with chronic hepatitis B in the United States are diagnosed and can access care and treatment to prevent cirrhosis and liver cancer. Universal screening offers a cost-effective, simplified, and nonstigmatizing way to identify people with hepatitis B. Additionally, universal screening with the three-test panel (HBsAg, HBsAb, HBcAb) will identify people who would benefit from vaccination as well as those at risk for reactivation. We strongly advocate for universal screening as the most effective and equitable testing strategy toward eliminating hepatitis B in the United States by 2030.

CONFLICT OF INTEREST

Nothing to report.

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Reply

We thank Dr. Cohen and colleagues for their interest in our manuscript, and for highlighting important issues surrounding HBV screening and advocating for universal screening.[1] Our manuscript was motivated by a desire to improve the status quo regarding HBV screening. Existing recommendations endorsed by the Centers for Disease Control are cumbersome and include stigmatizing information including illicit drug use history, human immunodeficiency virus status, and country of birth. We agree that the failures of risk-based screening are clear and may contribute to HBV infection underdiagnosis.[2]