BANK OF AMERICA INSTITUTE

BANK OF AMERICA

Transformation

First look: Healthcare breakthroughs

18 October 2024

Key takeaways

- The speed at which emerging technologies in healthcare will become realities is staggering. Recently, at the World Medical Innovation Forum, clinical experts, industry leaders and venture investors explored healthcare's medical, operational, and economic challenges in an effort to ensure that patients, providers, and healthcare organizations benefit as the healthcare landscape evolves.
- This year's event brought together 14 Harvard-affiliated Mass General Brigham clinicians and researchers to share "First Look" presentations highlighting their discoveries and insights on the next wave of breakthroughs in healthcare.
- With topics ranging from Alzheimer's Disease and counteracting age-related cognitive decline, to the promise of immunotherapy for brain cancer, experts shared high-impact technologies likely to disrupt healthcare in the coming months and years.

Healthcare innovations: The first look

Today, the speed at which emerging technologies in healthcare will become clinical realities impacting patient care is staggering. And accelerating the application of high impact technologies to the benefit of patients depends on everything from robust research practices to prudent leadership and smart partnering.

Recently, Bank of America joined Mass General Brigham to present the World Medical Innovation Forum, during which clinical experts, industry leaders and venture investors explored healthcare's medical, operational, and economic challenges to ensure that patients, providers, and healthcare organizations benefit as the healthcare landscape evolves.

This year, 14 Harvard-affiliated Mass General Brigham clinicians and researchers shared "First Look" presentations (click for more) highlighting their discoveries and insights on the next wave of breakthroughs in healthcare. With topics ranging from Alzheimer's Disease and counteracting age-related cognitive decline, to the promise of immunotherapy for brain cancer and safe AI, experts shared previews of high-impact technologies likely to disrupt healthcare in the coming months and years.

1. Microneedle drug delivery patch

Clinical need: Alopecia Areata (AA) is a T cell-mediated autoimmune skin disease that causes hair loss. The disease inflicts devastating social and psychological implications, yet more than 90% of alopecia patients – those with patchy or focal AA – remain without FDA-approved treatments.

Approach: The team engineered a novel microneedle (MN) patch for local and painless delivery of immunomodulators (CCL22 and IL2) that promote the recruitment and proliferation of regulatory T cells (Tregs). Bolstering Treg numbers at the site of autoimmunity can restore immune tolerance without the systemic off-target effects (e.g., immunosuppression) associated with conventional drug delivery methods.

Results: Experiments in murine immune-mediated AA models showed that CCL22+IL2 delivered via MN patch increased the frequency of Tregs in AA lesions and the absence of peripheral Treg expansion suggests that systemic immune function was maintained. This therapy led to a decrease in inflammatory markers and hair regrowth that persisted for months after treatment stopped.

2. "Snake" robotic bronchoscope

Clinical need: Lung cancer screenings can substantially improve survival outcomes, but rapid, definitive diagnosis of suspicious lung nodules is a critical unmet healthcare need. Unfortunately, the majority of lung nodules are in the periphery, and upper lobes are difficult to access via bronchoscopy.

Approach: The team developed a novel robotic bronchoscopic platform that "snakes" through airways in a flexible "follow-the-leader" fashion for accurate navigation, biopsy, and in situ intervention for lesions in challenging locations. They are exploring

autonomous capabilities to enhance clinical effectiveness, reduce cognitive and kinematic challenges for physicians, and shorten the learning curve.

Results: Through iterative prototyping and testing on pseudotumors in large animal *in vivo* studies (i.e., in a living organism) and *ex vivo* human lungs (i.e., outside of the living body), the team developed a platform that is optimized for ease of use, ergonomics, and minimal operating room footprint. Additionally, the superior maneuverability facilitates access to lesions in distal and upper lobe locations that were previously not reachable.

3. First-in-class proteasome inhibitors

Clinical need: Proteasomes work by "cleaning up" unwanted proteins in a cell, but this process can mutate and damage healthy cells instead. Proteasome inhibitors can mitigate these mutations, assisting in the treatment of multiple myeloma, also known as plasma cell myeloma. However, these drugs have significant limitations including therapeutic resistance and severe side effects ranging from nausea and diarrhea to insulin resistance and liver problems. Furthermore, although the proteasome has three different active sites, all three existing approved drugs target the same site.

Approach: PI31 is an endogenous protein inhibitor of the proteasome. The team discovered the inhibitory mechanism by which PI31 enters the proteasome and simultaneously inhibits all three active sites through direct interactions. This finding led to a new rational approach to develop proteasome inhibitors based on PI31's evolutionarily optimized mechanism.

Results: The team developed a series of potent and specific inhibitors. The lead molecule, ARFL-boronic acid (ARFL-boro), is highly effective *in vitro* (taking place outside a living organism, e.g., in a test tube) and in multiple myeloma cell lines. ARFL-boro shows strong synergistic activity with existing β5 inhibitors like Velcade. The team hypothesizes that such combination therapies could be useful in reducing rates of resistance and severe side effects. They tested ARFL-boro against 160 cancer cell lines and identified three other tumor types showing strong sensitivity.

4. Implantable brain-computer interface

Clinical need: Paralysis due to spinal cord injury, stroke, or ALS (Amyotrophic lateral sclerosis, also known as Lou Gherig's disease) is without a cure. However, implantable brain-computer interfaces (iBCIs) can restore lost neurologic function by using neurotechnology to reconnect disconnected parts of the nervous system.

Approach: Mass General Brigham and the BrainGate consortium are home to the longest-running clinical trial in iBCIs. The BrainGate system harnesses the cortical neural activity associated with the intent to move or speak.

Results: An ongoing study of the system has demonstrated an encouraging safety profile. It allowed people with tetraplegia or paralysis below the back that impacts all of a person's limbs, to control computers and move their hands intuitively by connecting to implanted simulators or soft, wearable robotics. Trial participants with ALS have also used BrainGate to 'speak' up to 62 words per minute.

5. Enhancing mental health using virtual reality

Clinical need: The mental health crisis among young people has steadily worsened over the past decade and mental health care systems are unable to meet the growing demand. Additionally, early detection and prevention strategies used in other fields of medicine have not been systematically adopted in psychiatry.

Approach: The team focused on the less severe and less differentiated earlier stages of psychopathology than current mental health programs, a strategy that may be more cost-effective and beneficial. They developed an immersive, multi-user virtual reality (VR) application to deliver a previously validated behavioral intervention called Resilience Training (RT). VR-RT includes six, one-hour sessions with up to 10 participants and two co-leaders. VR captures users' attention, simulates being physically near others, and provides accessibility and anonymity.

Results: Several studies of RT (conducted with >400 young people), including a randomized controlled trial, show that RT significantly improves emotional resilience and reduces subclinical symptoms of psychopathology such as depression and anxiety. Two pilot studies of VR-RT have yielded similar findings and demonstrate the additional benefit of increased social comfort and improvement in social perception – key components of healthy social functioning.

6. New treatments for lipid abnormalities in the brain

Clinical need: Nearly 7 million individuals in the US are living with Alzheimer's disease (AD), with the number increasing each year. The E4 variant of the apolipoprotein E (ApoE4) is the strongest genetic risk factor for developing Alzheimer's disease; it also significantly increases Lewy body dementia (LBD) risk and disease severity in Niemann Pick disease type C (NPC).

Approach: The complicated balance of lipids is pivotal for maintaining healthy brain function, and targeting lipid dysregulation is a paradigm shift towards treating neurodegenerative diseases, such as AD. In the brain, ApoE delivers lipids to neurons and glia. The team has developed a new human cellular platform in which dysregulated lipid and cholesterol transport is modeled in human cells by inhibiting endo-lysosomal transporter NPC1.

Results: The team used the platform to study the effects of ApoE isoforms on lipid accumulation in human cells (fibroblasts as well as neurons, astrocytes and microglia). Results show ApoE2 and ApoE3, but not ApoE4, reduce intracellular cholesterol levels, normalize levels of amyloid precursor protein (APP) and C-terminal fragments, and improve cell survival. Enhancing ApoE4 lipid transfer with an amphipathic lipopeptide corrected the function of ApoE4.

7. Reimagining precision oncology

Clinical need: Success in using precision-based approaches to inform treatment in modern oncology has been limited. Commercial biomarkers are based on a limited view of tumor biology and do not account for the role of tumor microenvironment (TME) in modulating therapeutic efficacy. Conventional approaches to evaluate the TME, such as RNA sequencing or proteomics, require tools that are not widely available in hospitals. Biomarkers that reflect a holistic view of interactions between tumor cells and TME could revolutionize precision oncology.

Approach: The team applied deep learning to extract and quantify diverse tumor and immune phenotypes from digitized hematoxylin and eosin (H&E) slides. They employed attention-based multiple instance learning on H&E whole slide images and bulk RNA sequencing data from core biopsies of breast cancer patients.

Results: Using binary classification, the team's trained model exceeded area under the receiver operating characteristic (AUROC) scores above 0.80 for most gene expression pathways, recognizing biologically relevant spatial patterns of cells in H&E whole slide images. Validation on a clinical trial dataset from triple-negative breast cancer patients is ongoing.

This model represents a first step towards developing computational H&E tools that reflect facets of TME biology and have potential to inform selection of more effective treatments for patients of virtually all tumor types. Given the wide availability of H&E slides, these tools fit into existing pathology lab workflows and can serve as a more readily accessible alternative to DNA/RNA sequencing for implementation of precision oncology.

8. Automating drug administration

Clinical need: Cesarean delivery is the most common surgery in the world, with approximately 19 million cases annually worldwide. Maternal and fetal safety depend on maintaining optimal maternal blood pressure; up to 75% of the patients are at risk for hypotension, a side effect of the anesthetic used.

And while optimizing drug infusion can significantly improve patient safety and outcomes, selecting the optimal dose to achieve the desired effect while avoiding under- or over-treatment is critical. The current standard of care in cesarean delivery involves monitoring vital signs and prophylactic vasopressor (phenylephrine) infusion with rate adjustment every minute. However, there are different physician approaches, and the process is error prone as individual patient responses to vasopressors vary.

Approach: The team's AI-powered platform can process real-time data in the operating room in a fast, resource-efficient way. They collected highly dimensional time-series data with precise times, vital signs, and doses of drug administration events from 172 patience in order to develop a highly accurate, Autoregressive with Exogenous Input (ARX) model.

Results: The ARX model predicts blood pressure changes up to three minutes in advance, a period sufficient to allow for physician intervention. The model performed 49% better than a mean constant model for one-minute-ahead predictions with a root mean square error (RMSE) of 3.6±1.3 mmHg (millimeters of mercury, a unit of pressure used to measure blood pressure). They anticipate that implementing machine learning can further enhance performance and personalize the results to individual patients.

9. Allogeneic naïve B cells

Clinical need: Cell-based approaches to regenerative medicine in the form of stem cell or progenitor cell therapies have been explored for over 40 years as a method of restoring tissue integrity and improving functional outcomes. However, a scalable approach that can successfully advance through FDA review for commercial use has yet to be developed.

Approach: Naïve B cells (NBCs) are fully developed, undifferentiated immune cells. Unlike stem cells, they are abundant and accessible, making up 60-70% of the B cells in the peripheral blood (over 5% of the white cells in circulation). Further, they are genetically stable and short-lived, promoting safety *in vivo*. The team has shown that when NBCs are placed into an injured tissue or infused intravenously in the context of CNS (central nervous system) injury or ALS, respectively, they can induce immune-regulatory, anti-inflammatory and neuroprotective – Regain – effects via multimodal mechanisms.

Results: The findings suggest that naïve B cells are capable of accelerating recovery from injury and promoting functional improvement, including neuroregeneration within injured tissue. Further, preclinical studies in mouse models of traumatic brain injury, intracranial hemorrhage (ICH) and ALS as well as initial first-in-human studies in two patients with ALS have demonstrated safety and potential to alter a subject's immune profile, elicit neuroprotection, and positively impact function. This study represents a first proof-of-concept showing the safety and feasibility of using NBCs as a therapeutic strategy for ALS.

10. Integrating patient-reported outcomes into routine care

Clinical need: Rheumatology, like many sub-specialties, is experiencing a demand-supply mismatch, with too few clinicians to serve patient demand. Providing care to patients at the appropriate time based on patient-reported outcomes (PROs) can improve efficiency, appointment availability and patient satisfaction.

Approach: RheumApp is a mobile health app that has been developed over six years through user-centered design with patients and clinicians. It allows patients to report symptoms periodically via brief, validated questionnaires. It's integrated into the clinical workflow through the electronic health record and helps clinicians use PRO data by applying logic-driven notifications when postponing a visit would be permissible or an early visit should be considered.

Results: Multiple studies demonstrate a 60-70% patient adherence with the application and over a one-year study, the app suggested delaying a visit for 86% of patients with rheumatoid arthritis. Through use thus far, 83% of patients would suggest that other patients use the app and over 75% of academic rheumatologists find it to be useful.

11. Using AI to streamline cardiovascular clinical trails

Clinical need: Randomized clinical trials represent the gold standard for establishing safety and efficacy, forming the basis for regulatory approval, clinical practice guidelines and payer coverage decisions. However, early and late-phase clinical trials have become large, complex, costly, and inefficient. For example, effective and safe endpoints require painstaking manual measurements of hundreds of parameters from cardiac imaging studies. Further, centralized adjudication (applying standardized criteria to participants' medical records) is costly, slow, and imperfectly reproducible.

Approach: The team has pioneered the use of cardiac imaging in cardiovascular drug and device development and use of imaging in clinical trials. The group has played a leading role in many international clinical trials in heart failure, hypertension and myocardial infarction. Recently, they have been exploring how novel AI technologies could automate and streamline the design and conduct of clinical trials, while carefully considering the risks of inaccuracy and bias in order to protect the validity of trial results.

Results: The team applied neural network-based segmentation and measuring tools to assess trial outcome measures. The AI tool is highly accurate when compared to human readers and offers greater reproducibility and efficiency. They have also developed a natural language processing model for adjudication. The initial model was trained to identify heart failure hospitalizations from discharge summary text on existing medical records and when the model was applied to international clinical trials, it yielded 87% agreement with human reviewers.

12. Multimodal, minimally invasive imaging for early disease detection

Clinical need: Screening tools for early disease detection and prediction can enable preemptive intervention. The team is developing technologies to detect atherosclerotic plaques in coronary arteries before they cause heart attacks and identify precancerous conditions like Barrett's Esophagus (BE).

Approach: Optical Coherence Tomography (OCT) provides high-resolution structural imaging but is sometime insufficient for accurate, early disease detection. The team combined OCT with fluorescence, which reveals chemical and molecular information for richer, more informative, and more clinically relevant imaging. Through collaboration, the team developed a multimodal imaging catheter combining OCT and near-infrared autofluorescence (NIRAF) imaging.

Results: The device is now being used in a clinical study assessing the role of OCT-NIRAF in managing coronary disease and aims to correlate NIRAF with plaque progression. In the future, inflammation-targeted molecular agents could be used to predict plaque risk even more accurately. Identifying such "vulnerable plaques" before a heart attack could provide a new personalized approach to coronary risk assessment and allow for optimized preemptive intervention, potentially saving many lives.

The team is also applying multimodal OCT to detect gastrointestinal cancers at their earliest stages. The current standard, endoscopy, is too invasive for broad-based screening due to the need for sedation. Thus, they developed OCT-tethered capsule endomicroscopy, a swallowable pill connected to an imaging system via a tether that captures 3D OCT images as it travels through the upper GI tract, a technology that has proven effective in detecting precancerous conditions.

13. Immersive, mixed reality medical education platform

Clinical need: Current medical training relies on opportunities to practice technical skills on real patients. Although medical simulators have been developed and marketed as a "bridge" to be used before first patient contact, these simulators have not been widely adopted as they are costly, require physical space, and are not readily adaptable to multiple medical specialties.

Approach: The team developed and validated mixed reality training modules that allow users to learn and practice technical skills in a fully immersive training environment. The modules work on low-cost, commercially available mixed reality headsets that can be widely disseminated and allow for self-directed practice and assessment. The modules also incorporate gamification of medical training to improve technical skills. The next step is to build a "medical holodeck" allowing for team training with multiple clinicians working in unison on a simulated clinical scenario.

Results: The team has conducted multiple studies on the use of virtual and augmented reality for medical education that show that mixed reality is a useful bridge to acquiring medical knowledge and technical skills in a safe environment. Early data from trials of the CT liver biopsy module suggest a strong correlation between trainees' scores in the mixed reality module with their technical proficiency as measured by standard assessment. Furthermore, the mixed reality module can potentially predict who is technically proficient for a particular medical procedure.

14. Non-invasive diagnosis of sepsis

Clinical need: Sepsis, a severe systemic response to infection, poses a significant risk to all newborn infants. In fact, the most commonly performed diagnostic test in the neonatal intensive care unit (NICU) is the "rule out sepsis" test, which requires a blood sample typically obtained by a heel stick. The procedure is painful and repeated tests can cause anemia. Additionally, the gold standard blood culture test is inaccurate and slow and in low- and middle-income countries, the test is frequently unavailable.

Approach: In the largest salivary study to date of 1,215 neonatal babies, the team identified a promising panel of 11 protein biomarkers and total protein in saliva to quickly and non-invasively identify sepsis.

Results: The team's biomarker panel enabled non-invasive sepsis diagnosis from saliva collected at a single timepoint with 77% sensitivity and 75% specificity – a two-fold improvement over standard of care. Saliva testing offers a non-invasive, pain-free, and safe alternative for detecting sepsis as well as an opportunity to minimize unnecessary antibiotic exposure in newborns.

Contributors

Vanessa Cook

Content Strategist, Bank of America Institute

Sources

2024 World Medical Innovation Forum / Mass General Brigham

September 23-25, 2024 - Boston, MA

1.Natalie Artzi, PhD

Associate Professor, Harvard Medical School; Head, Center for Structural Nanomedicine, Mass General Brigham Gene and Cell Therapy Institute (GTI); Core Faculty, Wyss Institute for Biologically-Inspired Engineering, Harvard University

2. Yolanda L. Colson, MD, PhD

Chief, Division of Thoracic Surgery, Massachusetts General Hospital; Hermes C. Grillo Professor of Surgery, Harvard Medical School

Nobuhiko Hata, PhD

Professor of Radiology, Harvard Medical School

3. John Hanna, MD, PhD

Pathologist and Principal Investigator, Brigham and Women's Hospital; Associate Professor of Pathology, Harvard Medical School

4. Leigh Hochberg, MD, PhD

Director, Center for Neurotechnology and Neurorecovery (CNTR), Massachusetts General Hospital; Senior Lecturer on Neurology, Harvard Medical School

5. Daphne J. Holt, MD, PhD

Director, Resilience and Prevention Program; Co-Director, Psychosis Clinical and Research Program, Massachusetts General Hospital; Associate Professor of Psychiatry, Harvard Medical School

6. Ole Isacson, MD, PhD

Founding Director, Neuroregeneration Research Institute, McLean Hospital; Professor of Neurology and Neuroscience, Harvard Medical School

7. Albert E. Kim, MD

Assistant Professor, Harvard Medical School; Assistant Physician, Massachusetts General Hospital Cancer Center; Investigator, Athinoula A. Martinos Center for Biomedical Imaging

8. Vesela Kovacheva, MD, PhD

Director Translational and Clinical Research in Obstetric Anesthesiology, Mass General Brigham; Assistant Professor, Harvard Medical School

9. Mark C. Poznansky, MD, PhD

Vaccine & Immunotherapy Center, Massachusetts General Hospital; Harvard Medical School

Ruxandra F. Sirbulescu, PhD

Vaccine & Immunotherapy Center, Massachusetts General Hospital; Harvard Medical School

10. Dan Solomon, MD, MPH

Liang Distinguished Chair, Professor of Medicine; Rheumatology, Brigham and Women's Hospital; Harvard Medical School

11. Scott D. Solomon, MD

Edward D. Frohlich Distinguished Chair, Professor of Medicine, Harvard Medical School; Senior Physician, Brigham and Women's Hospital

12. Guillermo Tearney, MD, PhD

Professor of Pathology, Harvard Medical School; Pathologist, Physicist, Massachusetts General Hospital

Farouc Jaffer, MD, PhD

Interventional Cardiologist and Director, Coronary Intervention, Massachusetts General Hospital

13. Raul N. Uppot, MD

Director, Mass General Brigham Medical Extended Reality (MXR) Lab; Interventional Radiologist, Massachusetts General Hospital; Associate Professor, Harvard Medical School

14. David Walt, PhD

Professor of Pathology, Brigham and Women's Hospital; Core Faculty, Wyss Institute at Harvard University; Hansjorg Wyss Professor of Biologically Inspired Engineering, Harvard Medical School; Howard Hughes Medical Institute Professor

Disclosures

These materials have been prepared by Bank of America Institute and are provided to you for general information purposes only. To the extent these materials reference Bank of America data, such materials are not intended to be reflective or indicative of, and should not be relied upon as, the results of operations, financial conditions or performance of Bank of America. Bank of America Institute is a think tank dedicated to uncovering powerful insights that move business and society forward. Drawing on data and resources from across the bank and the world, the Institute delivers important, original perspectives on the economy, sustainability and global transformation. Unless otherwise specifically stated, any views or opinions expressed herein are solely those of Bank of America Institute and any individual authors listed, and are not the product of the BofA Global Research department or any other department of Bank of America Corporation or its affiliates and/or subsidiaries (collectively Bank of America). The views in these materials may differ from the views and opinions expressed by the BofA Global Research department or other departments or divisions of Bank of America. Information has been obtained from sources believed to be reliable, but Bank of America does not warrant its completeness or accuracy. These materials do not make any claim regarding the sustainability of any product or service. Any discussion of sustainability is limited as set out herein. Views and estimates constitute our judgment as of the date of these materials and are subject to change without notice. The views expressed herein should not be construed as individual investment advice for any particular person and are not intended as recommendations of particular securities, financial instruments, strategies or banking services for a particular person. This material does not constitute an offer or an invitation by or on behalf of Bank of America to any person to buy or sell any security or financial instrument or engage in any banking service. Nothing in these materials constitutes investment, legal, accounting or tax advice.