



## 2023 AMA Research Challenge finals

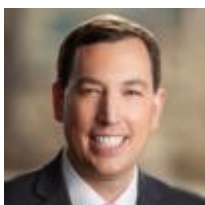


Jesse Kirkpatrick, a third-year medical student from Harvard School of Medicine, is the winner of the 2023 AMA Research Challenge and the grand prize of \$10,000, presented by Laurel Road.

- **Poster:** Detection of cholangiocarcinoma with protease activity probes (PDF)
- **Topic:** Basic Science
- **School:** Harvard Medical School

The judges announced the winner on Feb. 6 at the conclusion of the virtual research presentations from the finalists.

## Watch 5 finalists present research and compete to win



### Host

AMA President Jesse M. Ehrenfeld, MD, MPH

### Finalists

#### Alice Chen

- **Poster:** Effect of mesenchymal stromal cell delivery through cardiopulmonary bypass in a piglet model (PDF)
- **Topic:** Basic Science
- **School:** George Washington University School of Medicine & Health Sciences



## Jack Gomberg

- **Poster:** White Matter Markers for Treatment Outcomes in Major Depressive Disorder (PDF)
- **Topic:** Clinical and Translational Research
- **School:** Icahn School of Medicine Mount Sinai

## Jesse Kirkpatrick

- **Poster:** Detection of cholangiocarcinoma with protease activity probes (PDF)
- **Topic:** Basic Science
- **School:** Harvard Medical School

## Srujith Medharametla

- **Poster:** Effects of Obesity on the Neuromuscular Junction of Genioglossus Muscle and Other Associated Muscles of Respiration (PDF)
- **Topic:** Basic Science
- **School:** Chicago College of Osteopathic Medicine, Midwestern University

## Matthew Segar, MD

- **Poster:** Utilizing a ML-Enabled EMR Provider Workflow to Improve Non-Clinical Tasks (PDF)
- **Topic:** Health Systems Science
- **Institution:** Texas Heart Institute

## Panel of judges

### Kirsten Bibbins-Domingo, MD, PhD, MAS

Editor-in-chief, JAMA® and the JAMA Network™

### Frederick Chen, MD, MPH

AMA chief health & science officer

### Sanjay Desai, MD, MACP



AMA chief academic officer

## Transcript

**Dr. Ehrenfeld:** On behalf of the American Medical Association, welcome to the 2023 AMA Research Challenge. I'm Jesse Ehrenfeld, president of the AMA and your host for tonight's exciting event. For more than 20 years, the Research Challenge has showcased the best of the best in research conducted by medical students and residents. Tonight, we will continue that tradition when our judges select this year's winner of the AMA Research Challenge.

I can still remember the very first time I submitted an abstract for research competition when I was a second-year medical student at the University of Chicago. I was doing early work on the use of hand-held computing platforms in medical education. Going through the process of refining my ideas and figuring out how to communicate the work I was doing by writing up and submitting my first abstract was such an important step as I began to launch and develop my own research career, which has now led to the publication of more than 300 research manuscripts. We all have to start somewhere, and I am so thrilled that the AMA has provided this incredible opportunity for more than 20 years.

Now, before we get started, a little background on how we got to tonight's finals. As the largest event of its kind in the country, the AMA Research Challenge, for the third year in a row, has a \$10,000 grand prize on the line, and we want to thank Laurel Road for making this possible.

Not surprisingly, the challenge has once again generated incredible interest, enthusiasm and participation. We started with nearly 1,100 submissions, with 850 selected for presentation in our virtual poster symposium. The 40 top-scored posters then advanced to the semi-finals, where they were scored by judges and AMA members, which brings us to tonight's five finalists, an extraordinary group whose work represents the innovative thinking needed to continue to drive medicine forward. Please join me in wishing them all good luck as they compete for the AMA Research Challenge's \$10,000 grand prize. And again, thank you to Laurel Road for supporting medicine, research and our next generation of physicians.

In this final round of the research challenge, each finalist will have five minutes to present their idea to our panel of judges, who will determine our winner. Let's meet our distinguished judges, Dr. Kirsten Bibbins-Domingo, the editor-in-chief of JAMA® and the JAMA Network™, Dr. Freddy Chen, the AMA'S chief health and science officer, and Dr. Sanjay Desai, the AMA'S chief academic officer. Welcome, and thank you, judges, for being here.

Now, let's meet our incredible finalists who are ready to compete for this year's \$10,000 grand prize. Our first finalist is Alice Chen, a medical student pursuing a research year in between her third and



fourth year at George Washington School of Medicine and Health Sciences. Alice, what are your plans after you graduate medical school?

**Chen:** Yeah. So after graduating medical school, I plan to attend residency and hopefully continue my research opportunities there. I also have a secondary interest in global health, so I'm on the global health research track here at George Washington. I think it provides a great opportunity for cross-cultural understanding, which is something that's very important to me. It gives you the opportunity to bridge a lot of these cultural gaps that we see in the health care setting. So I think taking opportunities in my future career to expose myself to different health care systems and learn about different health care practices is a very important goal for me.

**Dr. Ehrenfeld:** Thank you, Alice. Our second finalist is Jack Gomberg, a third-year medical student from Icahn School of Medicine at Mount Sinai. Jack, what inspired you to go to medical school?

**Gomberg:** Yeah, great question. I have a little bit of an unorthodox way that I got to medical school. My first interaction in the hospital wasn't really as a patient, wasn't really as a volunteer. It was actually as a circus performer.

I've been in the circus since I was five years old, and when I was a teenager, I started performing in oncology and pediatric wards in the hospital, got exposed to patients that way. That kind of opened the doors to the medical world for me in a unique light. And I took that to combine with my interest in science, in research in stress, in research in neuroscience, and how we can best kind of combine the humanity and the science to better treat patients overall, and that's what I've been trying to do in my medical education. That's what I plan to do with my career.

**Dr. Ehrenfeld:** Thanks for being here, Jack. Next, Jesse Kirkpatrick, a third-year medical student at Harvard Medical School. How about you, Jesse? What inspired you to go to medical school?

**Kirkpatrick:** Well, I originally became interested in medicine because of a family member who was diagnosed with a liver disease called primary sclerosing cholangitis, which actually predisposes to the type of cancer that I'll be talking about in my presentation. And I originally became very interested in research and did a PhD. But during that time, what I realized was that what I really wanted to do was to take care of patients with this disease in addition to doing research on it, and so I decided to go to medical school.

**Dr. Ehrenfeld:** Great to have you here, Jesse. Now let's welcome Sruthi Medharametla, a second-year medical student at Chicago College of Osteopathic Medicine at Midwestern University. Sruthi, what keeps you motivated?

**Medharametla:** I mean, medical school can be tough, but I think for me, just learning about all the fascinating aspects of medicine, it's both the science and the art. I think it's incredible. That's what



keeps me motivated, to look at the end where I can go out there, be in the community, help these patients, form the professional relationships with the patients, and also learn from them. And at the same time, serve them when they need the physician most.

**Dr. Ehrenfeld:** Thank you, Srujith. And our final contestant, Matthew Segar, an MD and a cardiology fellow at the Texas Heart Institute. Dr. Segar, what inspired you to get involved in research?

**Dr. Segar:** Well, thank you. I think what I really appreciate and enjoy about research is seeing different problems around me in my day to day being a physician and thinking that there has to be a better way to do this. And so the best projects and research topics that I've come across are things that have affected me personally and have really inspired me to enact change, to make things not only better for myself but the people around me.

**Dr. Ehrenfeld:** Great. Thanks, Dr. Segar, and thank you to all of our finalists for being here today. Good luck, everybody, and let the AMA Research Challenge begin. First up is Alice Chen.

**Chen:** Hi, my name is Alice Chen, and I'm an MD candidate at the George Washington School of Medicine. Today, I'm excited to present my research that I conducted in the lab at Children's National Hospital on the effect of mesenchymal stromal cell delivery through cardiopulmonary bypass in a piglet model.

Congenital heart disease, or CHD, is the most commonly diagnosed congenital disorder in newborns. CHD is defined as a structural abnormality of the heart or great vessels that is present at birth. Even though many different investigations of its etiology have been conducted, the majority of CHD cases have not been attributed to a known cause.

Over the past few decades, mortality of complex forms of CHD has significantly decreased and has become more manageable with new surgical procedures. Despite these decreased surgical mortality rates, however, more children are developing neurological impairments, especially in those who require cardiac surgery, such as cardiopulmonary bypass or CPB. The etiology of these neurological deficits in CHD is both cumulative and multifactorial in part due to genetic factors and acquired risks from surgery.

This study focused on the perioperative phase, specifically looking into the effects of CPB surgery. CPB is a machine that can reoxygenate the blood and return it to the body to maintain the circulation even when the heart is stopped during surgery. But even though CPB allows us to maintain the circulation artificially, the blood is going through the tube without endothelial tissues, which can lead to systemic inflammation.

We've also known for quite some time that microglia, our body's resident phagocytic immune cells, play a key role when the brain is injured. They migrate towards sites of neuronal degeneration and

also alter their morphology dramatically in the context of disease.

On the other hand, we have mesenchymal stromal cells, or MSCs, which are multipotent non-hematopoietic cells that possess both immunomodulatory and regenerative properties that can treat a wide range of disease, including hypoxic brain injury. MSCs have been known to regulate microglial activation as well. So in this study, we hypothesized that intra-arterial MSC delivery through CPB is neuroprotective by modulating systemic and brain-specific inflammatory responses through reduced microglial expansion and activation.

So how did we conduct this study? To mimic these effects in young children, we randomly assigned two-week old female piglets to one of three treatment groups. First, we had six in the control group, four in the CPB group, and four in the CPB post-MSD treatment. CPB surgery was conducted for a total of 150 minutes followed by administration of MSCs before the weaning of CPB about 120 minutes into the procedure.

So to analyze the changes, we looked at the morphology. So morphological changes of microglia among all three of these treatment groups in the different cortical regions of the brain were assessed using a software program called Imaris by measuring changes in 1, the number of branch points from the nuclei itself, and 2, the lengths of microglia processes. We analyzed the activation of microglia through morphological changes since microglia are known to change shape from a more naive ramified to an amoeboid shape under activated condition.

So to identify the microglia, we used an antibody called Iba1 and then the activated microglia to just see the changes post-treatment. Those were detected with CD11b, which is a protein that can be used as a microglial marker for tissues derived from the nervous system.

So the results that we found are shown in these figures. So in figure 1, we see that CPB surgery reduced the number of branch points compared to control in all three cortex regions. In line with the hypothesis, as well, figure 2 shows that CPB reduced the lengths of processes in these cortical regions. And then these morphological changes were normalized after MSD delivery, as shown by the longer processes and increased number of branch points from the nuclei in the post-CPB plus MSD group.

So MSCs regulate microglial activation and participate in the phenotypic switch from a pro-inflammatory to the repair-permissive state. In contrast to their more ramified morphology, under normal conditions, activated microglia undergo structural remodeling, and they adopt an amoeboid morphology with highly retracted processes, which is a hallmark of brain inflammation.

Within the brain lesions of MSD-treated animals, there were significantly reduced numbers of amoeboid microglia and decreased levels of pro-inflammatory cytokines, which indicates an attenuated activation of the microglia associated, as well, with an increase in the number of branch

points and length of microbial processes to sort of mitigate the effects of CPB.

We also found that RNA sequencing of microglia derived from the lesions suggested that MSCs decrease the response of microglia to the ischemic insult. So clearly, from all the data that we've found, the significant differences between these two groups, the CPB and CPB plus MSC, points to the potential long-term benefits of MSC delivery. But while there were differences among the treatment groups, there weren't really any that were present within the specific regions of the cortex. So for future studies, it may be worth looking into the effects on white matter in the brain as well.

Also, examining the dose effect of MSC delivery, but comparing one dose, a standard dose that we used in this study, to a higher dose of MSC should be tested to optimize MSC treatment for children with CHD and to help elucidate the clinically significant outcomes for these patients in the future. Thank you.

**Dr. Ehrenfeld:** Thank you very much, Alice. And now to our judges for their comments. Who wants to lead us off today?

**Dr. Desai:** I can kick us off on this one. I have to say, the goals of the research are impressively ambitious. The idea of developing an intervention in such a complex system, where, again, we're looking at mesenchymal cells, the microglial cells, all the other components of the immune system, and the mechanical intervention of cardiopulmonary bypass to try to find an intervention that actually can affect outcomes there. I think it's quite ambitious. It's also, I think, because of that reason, also quite challenging to control for all the things that we would want to control for in this experiment.

**Dr. Bibbins-Domingo:** Yeah, I really liked the way the presenter both understood the very specific question that she and her team is looking at and was able to convey the results, but also then to define what the limitations are. We don't know everything after this very ambitious project, and to figure out what we do know and what we still need to know, I think she presented that really well.

**Dr. Chen:** Yeah, agree with both of my colleagues here. And it continues to amaze me sort of how much we are learning and still have to learn about inflammation and the role of inflammation in all of these disease processes. I thought the presentation was really nice. I thought the questions?like all good research?I think it really raises more questions than it was able to answer. It was a little bit tough to sort of get from the findings to congenital heart disease, I found, in terms of sort of connecting those dots, but impressive work, for sure.

**Dr. Desai:** If I could just build on what you're describing, I think the focus on inflammation makes this particularly exciting research because we have that same focus on inflammation related to bypass for so many other conditions. And bypass is such a common intervention that if we're even able to make modest improvement, then we can actually affect the lives of many, many more people.





**Dr. Ehrenfeld:** Well, great. Thank you for that feedback, judges. Really appreciate it. Let's go on to our next presentation, Jack Gomberg.

**Gomberg:** Hi. My name is Jack Gomberg. I'm a third-year medical student at Icahn School of Medicine here to present my research for white matter markers for treatment outcomes in major depressive disorder. Major depressive disorder, or MDD for short, is usually first treated with cognitive behavioral therapy or antidepressant medications like SSRIs. However, these treatments can work perfectly in one patient and have little to no effect in another. Right now, we have no way to predict what treatment will work for which patient.

A recent fMRI study showed a potential solution. They found that distinct patterns of functional connectivity from the subcallosal cingulate to the left anterior insula could predict which patients would get better on medication or therapy. In my project, I wanted to see if I could find a similar biomarker with white matter imaging, given current research points to the importance of white matter integrity in understanding depression circuit pathophysiology. This approach could expand on previous treatment selection biomarkers, and at the same time, reveal the structural underpinnings of functional findings in depression.

To test this hypothesis, we collected diffusion-weighted MRI brain scans from 167 treatment-naïve patients diagnosed with MDD. We then randomized them to 12 weeks of either therapy or antidepressant medication. We used the Hamilton Depression Rating Scale before and after to see if the treatment was a success or a failure.

We used these initial scans to create a white matter skeleton using tract-based spatial statistics. Each 3D pixel in this green skeleton has a value for white matter stability, which we call fractional anisotropy, FA for short. We can use these FA maps to run statistical analysis between patient groups and get regions of significant differences in white matter.

We carried out both correlation and two-by-two ANOVA interaction analysis. The correlation analysis will help us identify areas where greater white matter integrity as it's related to treatment success. And the ANOVA will highlight specific areas that can predict what treatment is best for what patients.

There are a few advantages to this approach. First, the analysis method was entirely data-driven. We examined white matter integrity in the whole brain with no previous assumptions. This avoided bias that might be introduced given the previous fMRI biomarker findings.

Furthermore, the findings here have greater potential for clinical adoption. Diffusion-weighted and FA imaging are structural scans, routinely acquired as part of a clinical brain MRI series and are more reproducible across scanners than fMRI.



Finally, white matter differences may lend important insight into how structural changes relate to functional patterns in depression, laying important insights for future treatment targets.

Let's first look at the correlation analysis. In green, we have areas that significantly correlate with improvement in depression scores, no matter the treatment. This means that higher white matter in the bilateral supplementary motor area, right mid-cingulate cortex, and right hippocampus generally correlated with better outcomes.

Next, we have red, representing medication and blue for therapy in group-specific correlations with improved outcomes. The SMA and ventromedial prefrontal cortex correlate with better treatment outcomes in patients assigned to medication, whereas the dorsolateral prefrontal cortex correlates with better outcomes for patients on therapy. These findings show that white matter can predict treatment-specific success. Furthermore, these regions are different in CBT, medication and overall groups which hints at important differences in the underlying mechanisms of treatment and outcomes.

Moving on to our two-by-two ANOVA interaction analysis, we cross-compared treatment success and failure for CBT and medication groups. The interaction effect showed the insula, the SMA, and the hippocampus as our significant regions of interest. The most exciting finding showed that same left anterior insula location from the functional connectivity paper. This reinforces the left interior insula as a potential imaging biomarker to better assign new MDD patients for medication or therapy.

Under the conclusion section, we can see our white matter findings next to the functional connectivity findings. More interestingly is that the white matter seems to predict treatment outcomes in the opposite direction as functional connectivity. For example, those that are predicted to do well on medication have high white matter stability but low functional connectivity to the left anterior insula. This lends an interesting relationship between the functional and structural changes in treatment and pathophysiology.

Overall, these findings offer a potential imaging strategy to personalize treatment for patients with depression rather than the current trial and error strategy. Our study further reveals a fascinating structural and functional relationship behind the disease. By better understanding how white matter plays a role in treatment outcomes, we can more fully understand how this disease progresses, how we can tailor treatments to individuals, and offer hope to those that need it most. Thank you.

**Dr. Ehrenfeld:** Thank you, Jack. OK, judges, time for your comments. Who wants to kick us off?

**Dr. Bibbins-Domingo:** Well, I'll start. First of all, this is a really important question, right? We want to know the right treatments for the right patients, and particularly for a disease like depression that affects so many.

What I really liked about the way that this young scientist approached this question is really addressing some of the pitfalls that can often take place in biomarker studies, right? He was very conscious of taking an unbiased approach, looking at the whole brain, not focusing on a particular area based on prior literature. He adopted an approach that might be scalable to other types of clinical settings, not just taking the most technical.

And then I think the most challenging, and sort of alluded to at the end, trying to link the finding with the actual function and the path of underlying pathophysiology. That's the hardest, of course, but I think paying attention to all three aspects, I think, was really remarkable in this study.

**Dr. Chen:** Yeah. And not just that, but also then taking that additional step, too, of treatment outcomes and trying to predict whether or not treatment is going to work or not for somebody. I mean, that is the bugaboo for us in clinical practice, and it is really an amazing part of the question. The whole piece kind of blew my mind around saying, let's find a structural, anatomic piece that might be predictive of this.

Because for us, depression treatment has really been about neurochemicals, right? And it's about fixing chemical imbalances. So to even consider that there's an anatomic piece of this that is somehow related to it and related to outcomes is super exciting.

**Dr. Desai:** Yeah. Just building on what both of you said, I found this fascinating. The clinical relevance is immediately available, but seeing someone at his stage being able to hold this fidelity to the science. So the idea of building on others' work, and then tying it to mechanisms and to structure and function, I thought, was really interesting.

The other interesting thing for me was just the idea of precision medicine. And so I think in many ways, precision medicine has not lived up to its promise in many different ways that it's been applied, and to see, again, young scientists, Kirsten, as you said, pursuing this space really, for me, makes it even more exciting, the promise of actually actualizing treatments based on precision medicine. So it was very enjoyable to listen to this.

**Dr. Ehrenfeld:** Well, thank you, judges, for the feedback. Let's get to our next contestant, Jesse Kirkpatrick.

**Kirkpatrick:** Hi. My name is Jesse Kirkpatrick, and I'm a medical student at Harvard. I want to tell you about cholangiocarcinoma, or bile duct cancer, which is one of the deadliest cancers in the world with five-year survival rates of less than 10%, on par with that of pancreatic cancer.

So here's the problem. The vast majority of bile duct tumors are detected at an advanced and incurable stage. One important reason is that existing diagnostic tools like MRI can't reliably distinguish early bile duct cancer from benign conditions like fibrosis, which severely hinders screening



in at-risk populations. What we really need is a diagnostic that can distinguish cancer from benign diseases, and that's where this project comes in.

So in this work, we leveraged a new class of diagnostic probes called activatable zymography probes, or AZPs, to detect cancer associated proteases. So why proteases? Well, proteases are enzymes that are dysregulated across cancers, including cholangiocarcinoma, playing key roles in invasion, angiogenesis, and metastasis, which makes them promising diagnostic targets.

So what are AZPs? Well, they consist of a positively charged and negatively charged peptide connected by a protease-cleavable substrate. Proteases in the tumor can cleave the substrate, allowing the positively charged peptide to bind to and light up the tissue.

So to model cholangiocarcinoma that arises on the background of biliary fibrosis, we leverage a mouse model in which two oncogenes, AKT and YAP, are overexpressed in the livers of the MDR2 knockout mouse model of fibrosis. We applied a library of 29 AZPs, which were designed to detect proteases that are commonly dysregulated in cancer to tissue sections from this model. When we applied one such probe, AZP6, to tissue sections from mice with just liver fibrosis, we saw no binding of the probe. In contrast, AZP6 specifically lit up cholangiocarcinoma tumors, and its binding was abrogated by the addition of protease inhibitors.

So of the 29 AZPs that we tested, we found five that bound preferentially to tumors relative to fibrosis, and two were even tumor-specific when compared to severe, advanced stage fibrosis. When we costained for AZP6 with cytokeratin 7, a marker for cholangiocytes, and vimentin, a marker for mesenchymal cells, we saw much stronger overlap of AZP6 with vimentin-positive cells.

In follow-up studies, we found that these mesenchymal cells are actually derived from epithelial cells, suggesting that our probes may be picking up proteases that are important for epithelial to mesenchymal transition, a hallmark of cholangiocarcinoma which is associated with chemoresistance and metastasis. We then apply these probes to a genetically distinct mouse model, this time driven by the oncogenes FBXW7 and AKT, and again saw cholangiocarcinoma tumor-specific labeling, demonstrating the generalizability of this approach across genetic subtypes of the disease.

And finally, when we injected a modified version of AZP6 into mice, we saw significantly increased uptake in tumor-bearing livers compared to fibrotic livers. Therefore, AZPs sensitively and specifically detect tumors in two genetically distinct mouse models of cholangiocarcinoma in a process that appears to be mediated by intratumoral mesenchymal cells.

Our next step will be to tag our AZPs with a radial label like copper 64, and perform preclinical PET imaging as a step toward clinical translation. Thank you.

**Dr. Ehrenfeld:** Thank you, Jesse. It's time to hear from our judges. Who wants to lead us off?

**Dr. Chen:** Gosh, I can start. I mean, first of all, I just thought Jesse's presentation was so excellent. I would love to listen to him lecture on biochemistry. It's much better than my experience was. So I thought that was really well done and very clearly presented.

I also think it's super interesting and super exciting where we are in this in this kind of work right now, how important work for biomarkers is to help identify these cancers that are so deadly and so difficult to identify with our existing means. I would love to see that next step that he alluded to, right? Let's start to see some of the clinical translation pieces of this and really get a better handle on where we are with it.

**Dr. Desai:** Yeah. I mean, you mentioned the biochemistry. For a young scientist, using the term, again, that Kirsten used, I think at this stage, to show such mastery over not just the clinical experience of this disease, but the research techniques that he described in such detail and applied them, these genomic techniques in such a sophisticated way, I found that very impressive.

**Dr. Bibbins-Domingo:** I think that first of all, I loved the images. So it's great for these types of?they're very visually compelling. But I think he's piecing together a complicated story, and to do it across different mouse models, to do it with staining and to show in general, but then to show the specificity, I think that's the way you build a story like this. And it's sort of painstaking work, and I really appreciated that he was able to bring that story to life. And then also to let us know what the next step for clinical translation is going to be moving from mouse then to where we ultimately want to be for the health of patients.

**Dr. Desai:** And the story. I appreciated the way he described the story currently. It's a sad one because we don't diagnose it early enough, and this research is exactly targeted at trying to help that survival benefit.

**Dr. Ehrenfeld:** Well, appreciate all of those comments and the feedback, judges. Next up, we've got Srujith Medharametla.

**Medharametla:** I'm Srujith Medharametla. I'm a second-year medical student at the Chicago College of Osteopathic Medicine. Obesity increases the risk of developing obstructive sleep apnea. Obstructive sleep apnea is a frequent breathing disorder characterized by repeated relaxation of the tongue and soft palate during sleep.

The genioglossus muscle, GG in short, is the largest extrinsic tongue muscle that is implicated in the pathogenesis of obstructive sleep apnea as it loses tone, falls back into the throat, and obstructs the airway. Our goal was to study the impact of obesity-induced obstructive sleep apnea on the neuromuscular junctions of the genioglossus muscle and some of the other muscles of respiration such as the diaphragm and the sternomastoid. We used leptin-deficient ob/ob mice as a model for our study because they show pharyngeal collapsibility, obesity, hypoventilation and hypercapnia

characteristic of obstructive sleep apnea.

Here is a diagram of the neuromuscular junction. It is an important site of communication between the nerve and the muscle. It is the best indicator of muscle function. In the diagram on the left, you can see that the neuromuscular junction is composed of different parts. We have the presynaptic axon terminals surrounded by the Schwann cell, coming close in contact?not touching, but in close contact?with the postsynaptic muscle membrane lined by acetylcholine receptors. Acetylcholine is the neurotransmitter released by the presynaptic axon terminal that then binds to the receptors and causes muscle contraction. By tagging fluorescent labeled bungarotoxin, we can tag acetylcholine receptors in the postsynaptic aspect of the muscle membrane depicted here on the right and measure the density of these receptors in the various muscles.

Looking at the density of these receptors and the genioglossus muscle to your far left, we can see that in the ob/ob group at 16 weeks of age, the ob/ob male mice showed a decrease in density compared to the wild type. We also saw a decrease at 20 weeks of age. The female mice tested around 16 and 20 weeks of age here to your right. At around 16 and 20 weeks of age, we observed no changes in receptor density between wild type and the ob/ob mice.

Using literature, we think this is possibly due to two mechanisms. The first possibility is that estrogen has a cardiovascular protective mechanism, and because neuromuscular junctions are highly irrigated by blood vessels, estrogen could be playing a protective role in these females. The second possibility is that estrogen is neuroprotective and prevents the disruption of lipid rafts in these female mice. Lipid rafts are microdomains of the skeletal muscle that are important for acetylcholine receptor clustering and also contain estrogen receptors, which may be used by estrogen to protect the junctions in these females.

Here are some of the images we got under the fluorescent microscope. We have wild type to the top and ob/ob male images at the bottom. The wild type at the top look sharp, well-assembled, but at the bottom, we can start to see the disassembly going on in the ob/ob male group and, also the appearance of pores marked here by the arrowheads.

Looking at some of the other muscles, we looked at the sternomastoid at 16 weeks of age. There was no change in receptor density, but at 20 weeks of age, we saw a decrease in receptor density in the ob/ob group. In the diaphragm muscle, we saw the opposite effect to that which was going on in the genioglossus muscle.

We observed an increase in density at both 16 and 20 weeks of age, suggesting a possible compensatory mechanism going on in the diaphragm given the loss of tone and the genioglossus muscle. Here are some of the example pictures we have of the wild type diaphragm and the ob/ob diaphragm, ob/ob looking better than the wild type, much more fluorescent. In the histology of the genioglossus muscle, we observed a significant increase in the presence of central nuclei in the GG

muscle of the ob/ob males. This is unusual for skeletal muscle, but it can be seen in both the H&E stained slides and electron microscopy slides.

We also observed fat infiltration starting coming in an H&E slide. Looking at muscle fiber type, we observed an increase in slow-twitch type 1 muscle fibers in the ob/ob group here on the right.

And looking at some of the images we acquired under the confocal microscope, we have wild type at the top, ob/ob at the bottom, red depicted by acetylcholine receptors, and the green and the blue depicting the presynaptic elements of the neuromuscular junction. We can start to see that the postsynaptic aspect is losing assembly. And also, the presynaptic green and blue, we can start to see morphological changes such as multiple innervation in axonal sprouting.

In conclusion, the GG muscle was affected in the male mice, not affected in the females. The sternomastoid was affected at 20 weeks of age. The diaphragm showed the opposite effect to that of GG at both 16 and 20 weeks.

The future direction of our study is to confirm, reproduce and increase some of the data on our data, and also to compare lipid rafts in both male and female mice that could help us clue into the physiology of sexual dimorphism. We would also like to take a look at stem cell markers that could help us understand histological changes. Thank you.

**Dr. Ehrenfeld:** Thanks so much, Srujith. Judges, back to you. Who wants to kick us off?

**Dr. Bibbins-Domingo:** Wow.

**Dr. Desai:** Please. Please. Please. So much to talk about here.

**Dr. Bibbins-Domingo:** I know. I know. I mean, obesity, obstructive sleep apnea, it's great. I mean, my favorite thing, of course, is just the fact that they have separated these mice by sex and see this really remarkable difference. And it just reminds me what the NIH has told us, that we have really not paid attention to differences in biology by sex. And that we're missing the opportunity not just to understand disease in half of the population, but also because we learn so much more about the mechanisms of disease when we really explore some of these differences. And it's really remarkable to see this big effect so different across the male and female mice. And I do wonder whether this group and this young scientist came in with that hypothesis, and whether he chose to look at that or just did it by happenstance. That was a question I had.

**Dr. Desai:** I think sort of same reaction in terms of the clinical conditions. So relevant for the world. As a pulmonologist, I always say we see our alarmingly increasing rate, and then obesity certainly globally. So the idea of someone stepping into the fundamental mechanisms of how those correlations and how they're connected is exciting, particularly using the biochemical and the physiologic





mechanisms that he's studying. I think that for me, one of the questions that emerged is the focus on estrogen. We know estrogen has so many actions, so it would be interesting in follow-up to understand what is the mechanism or what is the implication that estrogen has in the differences that you're highlighting between the sexes.

**Dr. Bibbins-Domingo:** Interesting.

**Dr. Chen:** Yeah. I mean, I also hit on those two same points. We think we understand sleep apnea and obesity. We know how closely related they are.

For me, it's like, isn't it just a mass effect kind of problem? But for them to start to ask this question of is it actually muscle weakness, is there actually a role there? I'm really challenged by the sex difference piece of it. I don't really understand why that model doesn't hold up for the two sexes, and that it raises more questions. But it also challenges the hypothesis too.

**Dr. Ehrenfeld:** All right. Well, judges, thank you for that. Now it's on to our final presentation from Dr. Matthew Segar.

**Dr. Segar:** Hey. My name is Matt Segar. I'm a cardiology fellow at the Texas Heart Institute. Thank you for the opportunity to talk about our work on leveraging machine learning to improve health care provider workflows. Before we delve into the intricacies of our solution, let's address the elephant in the room? physician burnout.

This phenomenon is far from trivial, affecting between a quarter to over half of primary care physicians. It's characterized by emotional exhaustion, depersonalization and a sense of reduced personal accomplishment. At the heart of this issue lies the continued burden of non-clinical tasks, which have steadily increased over time, often overshadowing patient care. Some of these non-clinical tasks, such as insurance paperwork as shown in the figure here, can add hours per month in increasing documentation demands.

It's this very challenge that set the stage for our research. In a health care landscape where efficiency is paramount and in-patient engagement is critical, how can we tip the scales back in favor of our health care providers? To address this knowledge gap, we hypothesized that machine learning, specifically natural language processing, could help streamline these non-clinical tasks to automate completion of insurance patient assessment forms.

To do this, we developed a methodological approach. We engineered a machine learning-enabled workflow with each step overcoming traditional barriers typically encountered in health care technology. First was EMR note extraction. Typically, each EMR system has its own unique architecture and data representation, which can be a formidable barrier to interoperability and integration.





To overcome this, we designed our note extraction process to be EMR agnostic. We employed a range of data exchange protocols such as HL7, FHIR, and even direct database queries whenever permitted. Regardless of the underlying technology, the module translated the retrieved data into a uniform structure for processing.

Second, we de-identified the data and removed protected health information. This maintained patient privacy in HIPAA regulations. Finally, we introduced natural language processing to interpret the notes and extract clinical insights and relevant ICD-10 codes for each patient encounter.

For example, a note may have a reported hemoglobin A1C of 7% with an estimated GFR of 56. While typical type 2 diabetes is coded as E11, our workflow would identify that additional kidney disease and recommend E11.22, type 2 diabetes with renal impairment. This process was improved by federated learning, which allowed our system to learn from each iteration and improve over time, all while keeping individual patient data localized and secure.

We then deployed our workflow in a real-world primary care clinic serving primarily Medicare Advantage beneficiaries. During the patient's annual wellness visit, physicians could review and approve each patient assessment form with a single click, and importantly, autogenerate screening orders for at-risk patients. After training our workflow on 6,000 synthetic notes, our workflow achieved a 10-fold cross-validation accuracy of 96%.

In a real-world suburban clinic, results were even better. Over a five-month period, patient assessment forms were completed for 179 patients and required only six hours of provider review time. Compare that to the prior months, it took three staff 30 hours to complete less than half the number of forms. This process resulted in significant cost savings and increased reimbursement for the clinic. But more importantly, it helped improve patient outcomes.

When looking at the highest-risk patients who had typically failed to complete necessary USPTF and society guideline screenings, we improved the number of preventative and diagnostic orders from seven-and-a-half orders per month to 24 orders per month, an over 200% improvement. The most common diagnostic test ordered was AAA scans with the ML workflow identifying patients with a prior history of smoking, age 65 to 75 years, who had never received the screening before. This was closely followed by transthoracic echocardiograms in patients with a history of coronary artery disease and progressive dyspnea who had not received one in upwards of six years.

In total, the system saw the percentage of gaps closed rising from 15% to over 25%. Importantly, the risk adjustment factor score, crucial for Medicare reimbursement, improved by 5%, indicating substantial fiscal and clinical benefits.

In conclusion, the integration of machine learning into health care workflows significantly improved operational efficiency, fiscal accountability and patient care management. Our findings suggest that



such systems can play a pivotal role in reducing health care costs and improving physician satisfaction, potentially reducing the burnout crisis.

**Dr. Ehrenfeld:** Thank you, Dr. Segar. OK, judges, time for your feedback. Who wants to kick us off?

**Dr. Chen:** Well, let me start, as a family doctor, having spent a lot of time on annual wellness visits and these patient assessment forms. And I absolutely resonate with the need to help streamline our processes and to help improve the work that can be done. So much of it can be done sort of via an automated piece. I think that's what this study shows, is that we can actually make these improvements.

If anything, I'm surprised we haven't seen more AI, machine learning stuff. I'm surprised that we haven't been replaced yet as judges, by AI. I think it's all coming in the potential, and the future changes are terrific. I think this was a nice study that really helps shines a light towards where we are going to go in clinical practice.

Still work to be done, right? I actually was a little bit underwhelmed with some of the percentage changes. I think that there's so much more potential that we can see from AI and ML in primary care and in administrative roles like this. But really a great start.

**Dr. Bibbins-Domingo:** Yeah, I agree. I think what I liked about the study, I think many people are thinking that ML, AI will have the greatest, more immediate potential in improving our workflows, improving the types of things that are both challenging for clinicians, but also ultimately don't yield the right results for patients, because ultimately, care is really being harmed because we don't fill out the forms and everything correctly. So I like the choice of question.

I like that they focused on the efficiencies but also the patient outcomes, because ultimately, that's what's going to be important. I think for a lot of these AI and ML studies, we are going to have to understand where does it fail us? Which patients are missing? Which types of clinical settings does it not work in?

And so I think that's going to be important, because there's a lot of enthusiasm, but these will not really also be perfect. We know that there are a lot of things that fail us in the way we've designed our health care interventions.

**Dr. Desai:** Yeah. I think building on both, so it also struck me that the incremental benefit was modest in this, but I also recognize that we're very early in this. And there's a tremendous benefit to scale here.

And so I'm impressed with a couple of things. One is just taking on physician burnout. This is an existential threat, I think, to our profession, so to have people investigating this and how to improve it



is really important.

And then I think also we underestimate how challenging it is to break those interoperability barriers that this team has broken. So I feel like for all these reasons, we're just early in this, and we have so much more to learn, but this, I think, showcases some of the promise that we have with ML, AI, NLP, all of these different technologies that hopefully can be extended from the research that that's been presented to actually start to measure burnout, to start to measure well-being, start to measure patient outcomes as suggested for the hopefully near future, not too distant future.

**Dr. Ehrenfeld:** Well, great. Thank you, judges, for your comments and discussion on all five of the presentations. Let's also give a huge hand to all our finalists for their outstanding research and work on their amazing presentations. Congratulations to all five of the finalists.

Well, now it's decision time for our judges. They've got a tough choice to make in deciding this year's winner. Judges, let's get your final thoughts on crowning our 2023 AMA Research Challenge winner. Who wants to kick us off?

**Dr. Desai:** I can start for the group. Well, first, just congratulations to everyone. This is a remarkable group of researchers that have presented. Not only performed the research, but then presented it in such compelling ways.

As I reflect on the presentations, I think one challenge, particularly given the fact that we're asking people to do this in five minutes and to an audience that isn't as well-versed, often, in the science or the techniques being presented, it's often challenging to bring somebody along in the thought process of the science in a way that takes you from step A to step B, and then by the conclusion, you're there on the same journey with the person presenting, and that's hard. And I think when that's not done effectively, there are leaps that have to occur, and I think trying best to make that journey seamless is really important.

**Dr. Chen:** Yeah, I want to echo that. Such an impressive group from a huge group of submissions. And to be able to see this level of complexity of research, of high-level questions, of important questions, that makes choosing and deciding and judging really hard.

I think at this point, a specific point is I thought some of the visuals were very helpful. And it was actually great to see the different types of visuals that were presented. But to Sanjay, your point, the visuals are only as good as being able to link to those, help people understand that thought process and connect those dots, because these are such complex ideas that we're doing research on. To sort bring people from sometimes cellular mechanisms all the way to disease processes and treatments, it's really tough.



**Dr. Bibbins-Domingo:** Yeah. Yeah. I just wanted to also underscore just how impressive the presentations were. One of the things that I would highlight as important, I think, in the scientific process is that presenters also understand the limitations of what they're doing, right? Because the limitations end up helping us to both understand the science. I think they convey to the audience that you have a deep understanding of what you've done, because you also understand what it didn't tell you.

I think there's a tendency early on to think that this is all about how great everything is, that you've come to the conclusion. All of the presenters did a great job, and I think the ones that did a particularly compelling job are the ones who are able to say, well, you know, we're falling short here, and this is the limitation of what we found.

I would say, to me, one of the things that's really impressive in all of this is that we're asking people really early on in their careers to have a strong clinical insight, but also to think like a scientist, and then to be an exceptional communicator, right, to be able to tell us, this is the broad question we're interested in. This is the clinical context. But then here are the things that this specific experiment was able to tell us and what it wasn't able to tell us.

And then as you all said, to take the listener or the reader on the journey along the way. And I think that's what we certainly think about all the time with the journals and at JAMA® and the JAMA Network™. But it is one of the things that I love to see people early in their careers already starting to think about, and it's those three skills?an outstanding clinician, an outstanding scientist, and an outstanding communicator of the science and the context. They're hard to get, and it's great to see five people well on their way to doing this.

**Dr. Chen:** It's amazing.

**Dr. Desai:** Just listening to the challenges that we all described, it's even more impressive what they've done, because just reflecting personally on my experience, I was so far away from being able to do these things at the level that these five finalists have been able to do and showcase to us.

**Dr. Ehrenfeld:** Well, you all certainly have a tough task ahead. These were five fantastic presentations, but you have to pick a winner. So we're going to give you a few minutes and then come back to get your final decision.

OK, it's time to check back in with our judges and get your final thoughts on the winner of the 2023 AMA Research Challenge. Judges?

**Dr. Bibbins-Domingo:** Well, my colleagues have given me that wonderful task of announcing the winner. First of all, congratulations to all five wonderful presenters. Congratulations on your work, and keep it up. It's really exciting.



But the presentation and the science that stood out amongst this really outstanding set of presentations is that of Jesse Kirkpatrick, who presented his work on detection of cholangiocarcinoma with protease activity probes. So I'll invite my colleagues to talk about why we chose this work.

**Dr. Chen:** I just thought Jesse did such a nice job presenting his research in helping us through visuals and then talking, sort of leading us along that path from the very basic molecular level all the way to the disease state and the challenges of it. It was really easy to follow. It was really clearly well done.

**Dr. Desai:** Yeah, and I think that ability to convey at that detail and take us on that journey reflects the mastery that Jesse has over both the clinical content as well as the science that was conducted, for three people that are not treating patients with cholangiocarcinoma every day. And so I think that foundation across the clinical disciplines, the science disciplines, and then take us on that journey? again, so impressive.

**Dr. Ehrenfeld:** Well, perfect. Thanks for your decision, and thank you so much for participating in the judging process for our AMA Research Challenge. We couldn't have done it without you.

And now we've come to a very exciting part of the show where we tell the winner the big news live. We just called Jesse Kirkpatrick, and he has no idea that he has won. Let's bring him on and tell him the great news.

Hi, Jesse. This is Jesse Ehrenfeld, president of the American Medical Association. How are you doing today?

**Kirkpatrick:** I'm doing great, thanks. How are you doing?

**Dr. Ehrenfeld:** Awesome. Awesome. Well, it's great to see you. Thank you for giving us some of your time today. We just finished speaking with our panel of judges, and I've got one more question for you that we need to know. Jesse, how does it feel to be the winner of the 2023 AMA Research Challenge with a grand prize of \$10,000?

**Kirkpatrick:** I cannot believe this. I am speechless. I'm extremely grateful, and I just think about how thrilled the members of this rare disease community that I'm a part of and that I work with, PSE partners, how supportive they were when they found out that I was a finalist, because it meant that they really care about a rare disease like this, which is attention that they've never really gotten before. And the fact that I've been selected just means so much to me, and I know that it's going to mean a ton to that community as well.

**Dr. Ehrenfeld:** Well, certainly you, your research, this community are getting some attention today. Did you ever think when you first entered the competition that you'd leave as the big winner?



**Kirkpatrick:** Absolutely not. I had known from watching previous years' Research Challenge finals that the competition is extremely stiff. I knew that there were going to be hundreds or even more applicants, and I knew how incredible the research was that I was going up against. So I had no idea in my wildest dreams, and I'm just incredibly grateful.

**Dr. Ehrenfeld:** Well, it wasn't hundreds. It was thousands of applicants this year.

**Kirkpatrick:** Wow.

**Dr. Ehrenfeld:** We had a record number of submissions. I know research is a team effort. Is there anybody that you'd like to kind of give a special shout out to?

**Kirkpatrick:** Absolutely. I mean, I have to start by thanking my advisor, Dr. Sangeeta Bhatia, who has been so incredibly supportive, has given me the opportunity to really pursue my dreams and work on research that I never thought that I'd be able to really work on. And then I also want to thank the Resnick Center at Brigham and Women's Hospital and Frank and Barbara Resnick for their incredible generosity in supporting work related to primary sclerosing cholangitis.

And I also want to just thank all my collaborators at Beth Israel, Yuri Popov and his lab. And I also, of course, just want to extend a huge thank you to the AMA and to the sponsors of this competition.

**Dr. Ehrenfeld:** Well, we are really lucky to have Laurel Road provide that \$10,000 grand prize. Have you thought about what you might do with the money?

**Kirkpatrick:** I mean, it's a very large sum of money. I'm going to have to do some processing. I think that it's going to go a long way in helping me with some of my medical school loans, which is going to be hugely impactful.

As I think about wanting to have a career as a physician scientist, this additional support will be something that allows me to really focus on the things that matter to me, like the research that I want to work on. So I think that that's probably going to be where the bulk of it goes. And of course, some of it might go to feed my cat and vet bills, and hopefully some vacation as well.

**Dr. Ehrenfeld:** What's your cat's name?

**Kirkpatrick:** His name is Oscar. He's meowing around here right now. I think he knows that something good has happened.

**Dr. Ehrenfeld:** Awesome. Well, you and Oscar definitely should be celebrating today. Jesse, thank you for being here. Thank you for your research, your passion for trying to advance human health, and again, congratulations. I hope that you continue your journey in research, and we can't wait to see what you do in the future.



**Kirkpatrick:** Thank you so much.

**Dr. Ehrenfeld:** Congratulations to all our finalists and to our 2023 AMA Research Challenge winner, Jesse Kirkpatrick. Such impressive and innovative work was demonstrated here today, and indeed throughout this year's challenge. On behalf of the entire AMA, I again thank all of the participants, co-authors and mentors for your contributions to research and this year's projects. And again, a huge thank you to Laurel Road.

On a personal note, my interest and passion for research began in medical school and residency and continues to this day in the field of biomedical informatics. I only tell you this because it's my hope that you, too, will continue to have a strong interest in research, for it is research that moves medicine and science forward. It gives us data and insights that drive innovation and new methodologies and treatments that result in better outcomes for our patients.

Research makes us better physicians. Thank you for tuning in and being a part of this great event. Have a good night.