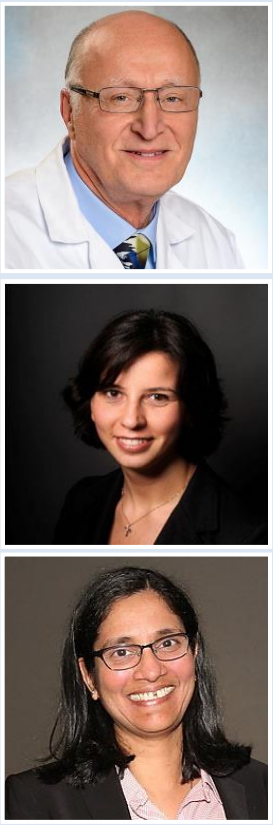
BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL

Life. Giving. Breakthroughs.

Advancing Cardiac Amyloidosis Research and Care

Thanks in part to your generous support through the Sean McDonough Celebrity Golf Classic Fund For Cardiac Amyloidosis, the Amyloidosis Program at Brigham and Women's Hospital continues to offer outstanding clinical care, advance innovative research on new treatments and diagnostic approaches, and increase awareness of amyloidosis on a global basis. Renowned program director and cardiologist **Rodney Falk, MD,** leads a multidisciplinary team of specialists that includes associate director and oncologist **Giada Bianchi, MD,** and cardiac imaging expert **Sharmila Dorbala, MD, MPH**.



The powerhouse team behind the Brigham Amyloidosis Program. Top to bottom: Rodney Falk, MD, Giada Bianchi, MD, and Sharmila Dorbala, MD, MPH.

It is a testament to its growing international recognition that the Brigham Amyloidosis Program attracts patients from around the world. Some are seen in person in Boston, while others receive virtual consultations through the program's new telehealth capability. In the last year, Dr. Falk and his team have seen patients from Austria, Canada, Israel, New Zealand, and Saudi Arabia, in addition to the United States.

Through their dedicated efforts, Dr. Falk and his team have helped to transform this once-fatal disease into a condition that can be slowed and sometimes even cured. As you read the following updates on the Amyloidosis Program, we hope you take great pride in all that your generosity helps make possible.

New Options for Treating Amyloidosis

This past year, Dr. Falk and his team continued to lead groundbreaking trials to evaluate the effectiveness of a new generation of drugs to treat transthyretin (TTR) amyloidosis, which causes amyloid deposits to build up in multiple organs in the body, particularly the heart.

- **"Silencer" Drugs:** This family of drugs, including inotersen (Ionis Pharmaceuticals) and patisiran (Alnylam Pharmaceuticals), slow or even halt the progression of amyloidosis by reducing levels of TTR protein in the body. The FDA has approved both drugs for the treatment of familial amyloid neuropathy (a disease of the nervous system). Now, Dr. Falk and his team are not only using these drugs in clinical practice for amyloid nerve

damage but also conducting research to determine if inotersen can also slow the progression of cardiac TTR amyloidosis.

Dr. Falk has launched a phase 2 study of **inotersen** that includes patients with the genetic form of cardiac TTR amyloidosis ("familial") and those who develop it with age ("wild-type"). Early results have been promising. Inotersen is well tolerated, and the drug lowered levels of TTR protein by 70 to 80 percent. Regular cardiac imaging studies are performed in this cohort of patients to see if inotersen can slow or even halt the disease.

The Brigham will also be participating in the HELIOS-B study, a phase 3 multicenter clinical trial of **vutrisiran**, a TTR silencing drug that only needs to be administered every three months, to determine whether this drug can help patients with cardiac TTR amyloidosis. Dr. Falk and his team hope to begin patient recruitment soon.

- **Tafamidis:** In May, tafamidis (Pfizer, Inc.), became the first FDA-approved treatment for TTR amyloidosis. The drug slows the progression of TTR amyloidosis by stabilizing TTR protein, preventing it from breaking down to form amyloid deposits. Although tafamidis is now commercially available, the administrative hurdles to prescribe the drug, as well as its cost, have been daunting. To address these issues and improve accessibility for patients, Dr. Falk worked with the Partners HealthCare Specialty Pharmacy to streamline the prescription process and identify medical foundations to cover the cost for patients who need financial assistance. The new system has been enormously helpful to nearly 100 patients to whom it has been prescribed to date, while saving physician time that is better spent caring for patients or conducting research. Data addressing the cost and accessibility of tafamidis were recently presented by Dr. Sarah Cuddy on behalf of the Brigham Amyloidosis Program at an international conference on TTR amyloidosis held in Berlin, Germany.

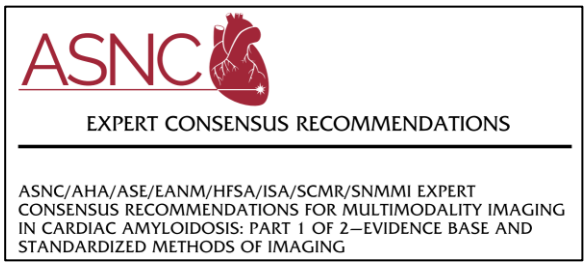
Improving the Diagnosis of Amyloidosis

One of the most exciting developments in the field has been the improvement of noninvasive imaging techniques to enable earlier and more accurate diagnosis of cardiac amyloidosis. In many cases, patients can now be diagnosed with imaging alone and no longer need to undergo invasive cardiac biopsy. Dr. Dorbala continues to advance research in this area.

First Consensus Guidelines for Diagnostic Imaging in Cardiac Amyloidosis

Relatively few physicians are experts in diagnosing cardiac amyloidosis or understand all of the options available for evaluating patients who may have the disease. To address this

worldwide knowledge gap, Dr. Dorbala chaired a panel of experts from leading organizations from around the world who developed consensus guidelines on how to use noninvasive imaging as part of a thorough patient evaluation. The two-part guidelines detail the diagnostic criteria for cardiac amyloidosis, advise what symptoms and conditions merit further investigation, and provide the first-ever guidance on how to standardize the use of techniques such as echocardiography, magnetic resonance imaging (MRI), positron emission tomography (PET), and radionuclide imaging, either alone or in combination with cardiac biopsy.



Endorsed by multiple international medical organizations, including the American Heart Association, and published in August 2019 in both the *Journal of Cardiac Failure* and the *Journal of Nuclear Cardiology*, the guidelines represent a major achievement by Dr. Dorbala and the consensus committee. Through their wide dissemination in the medical community, the guidelines will improve the diagnosis and treatment of cardiac amyloidosis now and for years to come.

Expanding the Use of Noninvasive Imaging

Dr. Dorbala was among the first investigators to show that ^{18}F-florbetapir, an imaging agent used in PET scans that was originally FDA approved to detect amyloid plaques in the brain, could also detect amyloid in the heart. Drs. Dorbala and Falk are now leading a multi-year clinical study to evaluate whether ^{18}F-florbetapir can quantify cardiac amyloidosis activity, and whether this imaging agent can be used to assess the impact of treatment over time.

Dr. Dorbala is also investigating whether noninvasive imaging enhanced by ^{18}F-florbetapir can detect amyloid deposits in other parts of the body. She authored a paper published in September in the *Journal of Nuclear Medicine* which showed that ^{18}F-florbetapir-enhanced PET and CT imaging helped identify amyloid deposits in the parotid gland, tongue, lungs, kidneys, and abdominal wall. This was significant because the enhanced imaging revealed amyloid deposits *before* patients developed symptoms. Such early detection could help physicians tailor treatment to each patient's unique biology, as well as guide disease management.

Advancing Lab Research on AL Amyloidosis

Amyloid light-chain (AL) amyloidosis, a blood-based disorder, is the most common and life-threatening subtype of amyloidosis. It responds to chemotherapy and other drug treatments that are used for a related disease, multiple myeloma. Dr. Bianchi is a specialist in multiple myeloma at Dana-Farber Cancer Institute and brings valuable expertise in this area to the

Brigham's Amyloidosis Program. Since joining the program as associate director last year, Dr. Bianchi has streamlined the process of evaluating patients for AL amyloidosis, ensuring earlier and more accurate diagnosis, as well as appropriate coordinated treatment.

Inspired by the targeted therapies that have revolutionized cancer treatment in recent years, Dr. Bianchi is also working to develop more effective therapies for AL amyloidosis. Currently, she is investigating novel molecular targets and therapeutic approaches to halt light chain secretions and induce death of amyloidosis cells. Her lab is also investigating the mechanisms underlying resistance to currently available therapies for AL amyloidosis in order to develop novel drugs to overcome clinical resistance and ultimately improve patient survival.

In addition, an exciting project in Dr. Bianchi's lab is focused on identifying the process that enables a precursor condition known as "monoclonal gammopathy of undetermined significance" to evolve into AL amyloidosis or multiple myeloma. By analyzing the molecular steps in this evolution, she hopes to identify new targets for drug therapies that can interrupt and possibly prevent disease progression.

Educating Physicians and Patients about Amyloidosis

The Amyloidosis Program is committed to raising awareness of amyloidosis among physicians and patients. This year, the team helped to advance knowledge in a variety of ways.

Participating in International Conferences

Drs. Falk and Dorbala regularly attend international medical conferences to share the latest insights on amyloidosis. Last March, Dr. Falk presented at an Amyloidosis Conference for Hematologists, Cardiologists, Nephrologists, and Neurologists in Israel. In September, he spoke at the Second European Conference for TTR Amyloidosis in Berlin. And in March 2020, he and several members of the team will attend the International Symposium on Amyloidosis in Spain.

Dr. Dorbala spoke about amyloidosis imaging in August 2018 at the Brazilian Congress of Nuclear Medicine, São Paolo, Brazil; in October 2018 at the European Association of Nuclear Medicine, Dusseldorf, Germany; in April 2019 at the Chinese Society of Nuclear Cardiology, Beijing, China; and in May 2019 at the International Congress of Nuclear Cardiology and Cardiac CT, Lisbon, Portugal.

Educational Materials for International Physicians

Dr. Dorbala chaired a writing group that developed a document for practicing physicians about bone tracer imaging for TTR cardiac amyloidosis: American Society of Nuclear Cardiology, ASNC Cardiac Amyloidosis Practice Points. This document is a resource for physicians

worldwide, is distributed in Europe in collaboration with the European Association of Nuclear Medicine, and is now being translated into Spanish, Portuguese, and Chinese.

Publishing Research Findings in Scientific Journals

Dr. Dorbala was senior author of a paper published in June in the journal *Circulation: Heart Failure* that provided the first epidemiological estimates of the incidence (number of people diagnosed per year) and prevalence (total number of people with the disease at a specific point in time) of cardiac amyloidosis in the United States. The team examined national Medicare data for patients 65 and older who were hospitalized at least once for cardiac amyloidosis over a 10-year period (2002 to 2012).

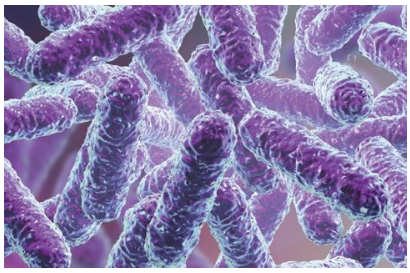
The researchers found that the incidence of cardiac amyloidosis doubled during that period, while prevalence tripled. These trends were particularly striking in the Northeast and in Minnesota—two geographic areas that are home to academic medical centers with experts in amyloidosis. This suggests that increased awareness of cardiac amyloidosis, combined with advanced noninvasive imaging, has led to an increased number of diagnoses. Moreover, increases in prevalence (which indicates people are living longer with the disease) suggest that improved treatments are extending lives. Given these trends, the authors recommend that physicians consider cardiac amyloidosis as a possible diagnosis when a patient 65 and older develops heart failure or shows other symptoms of the disease.

Helping People Understand Genetic Test Results

The wide availability of direct-to-consumer genetic testing from companies such as 23andMe has made it easier for people to learn whether they have mutations for a wide range of diseases, including amyloidosis. Currently, 23andMe offers screening for three of the most common amyloid-related mutations. This presents a challenging situation: how to provide accurate, timely information to help people understand their test results and determine next steps.
To address this issue, Dr. Falk is working with 23andMe to produce an educational video that describes what cardiac amyloidosis is, what it means to test positive for an amyloid-related mutation, and possible next steps to consider, including contacting the Brigham for more information or an appointment, or requesting a referral to a local specialist (for people who live outside of Boston). The video will be posted on the Brigham website and shared by 23andMe with anyone who has screened positive for an amyloid-related mutation.

Exploring the Impact of the Microbiome in Amyloidosis

Dr. Dorbala and her team have secured funding from Pfizer for TTR amyloidosis and from the American Heart Association for AL amyloidosis (co-led by **Ronglih Liao, PhD**), to study the gut microbiome of patients with AL amyloidosis and TTR amyloidosis. The gut microbiome—


Intestinal microbiota

the complex collection of bacteria, viruses, and fungi that lives in the digestive tract—has been the focus of much research, as scientists have learned that these usually friendly colonies aid in metabolism, digestion, and health, but can also contribute to disease. Dr. Dorbala plans to launch an observational study, in collaboration with the Human Microbiome Core Laboratory at the Harvard School of Public Health, to compare how the gut microbiome in people with amyloidosis differs from that in healthy people. Future research may investigate how amyloid deposits affect specific gut microbes, and vice versa, to determine whether alterations in gut microbes predispose an individual to develop amyloidosis. Ultimately, this new line of inquiry may lead to the development of a simple screening tool to identify individuals at risk for amyloidosis.

The Impact of Your Support

Thanks to your exceptional support, Dr. Falk and his colleagues are leveraging state-of-the-art technology and research approaches to expand our knowledge about amyloidosis, paving the way to new diagnostic, prevention, and treatment options for this complex disease. Your philanthropy has played a critical role in these efforts, and we are truly grateful. On behalf of our entire staff, as well as the many patients and families who benefit from this work, thank you once again for your generosity and partnership.