

**Article:**

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**Guests:** Drs. Sæmundur Rögnvaldsson and Sigurður Yngvi Kristinsson from the University of Iceland, both working on the the iStopMM screening study.

Bob Barrett:

This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Multiple myeloma is the second most common blood cancer with incidence increasing as the age of the global population increases. Despite advances in treatment, myeloma remains a significant cause of morbidity and mortality. In an effort to improve outcomes and extend life expectancy for affected patients, some have advocated population screening programs to catch myeloma in its early stages prior to the development of significant organ damage. Others have pointed out that early detection does little to improve outcomes and initiation of early treatment actually does more harm than good. So how should we proceed? Is myeloma screening likely to help patients or will it simply cause unnecessary anxiety while adding healthcare cost?

A review article appearing in the January 2024 issue of *Clinical Chemistry* summarizes the potential benefits and harms of multiple myeloma screening and recommends next steps for clinicians and laboratorians to move the field forward. In this podcast, we are pleased to welcome the lead and senior authors of the review article. Dr. Sæmundur Rögnvaldsson is a physician and postdoctoral researcher at the University of Iceland. He has been deeply involved in the design and implementation of the iStopMM screening study with the aim of determining the potential benefits and harms of MGUS screening. Dr. Sigurður Kristinsson is a professor in hematology at the University of Iceland and the principal investigator for the iStopMM screening study. So, Dr. Rögnvaldsson, we'll start with you. Monoclonal gammopathy of undetermined significance, or MGUS, is a benign condition with a low risk of progression, so why should we even be interested in this phenomenon?

Sæmundur  
Rögnvaldsson:

This is actually an excellent question. I think there are two sides to that issue. Number one, it's clinically interesting because it's the precursor of multiple myeloma and other clinically significant disorders. It is a low risk of progression. However, these disorders, especially multiple myeloma, are quite serious, and we know that multiple myeloma often presents in a very acute setting with severe renal failure,

fractures, and so on, which sort of limits our ability to apply effective therapies and leads to early mortality. However, this acute disease develops over years, even decades, from this precursor.

Now there's this MGUS, and then most people go through a second phase called smoldering myeloma, and some recent studies have actually shown that if we treat people at this still asymptomatic stage, we can possibly prevent them from developing active myeloma, which is a pretty devastating disease. But these precursors are all asymptomatic and only 5% of those, or around 5% of those, who develop myeloma actually know about a precursor condition. So 95% or thereabouts of those who get myeloma have no possibility of ever getting early treatment. So that's where MGUS is interesting, because MGUS is easily detectable in blood and the question is, can we screen for MGUS, detect this disease early, follow people, and then intervene early and improve outcomes? So that's sort of the clinical aspect of it. That's why MGUS is interesting from a clinical point of view. But secondly, MGUS is also very interesting from a biological point of view.

Myeloma is a little bit unusual in that very early on, we have very overt signs of the disease in the blood, that is MGUS, because MGUS is this presence of monoclonal antibodies or monoclonal free light chains in the serum, which is often detectable even years or decades, as I mentioned earlier, before developing myeloma. So we have there an opportunity to watch the development and the birth of this malignancy, really in real time when we study MGUS. So from a biological and a translational standpoint, MGUS is also a very interesting phenomenon where we can study how myeloma really develops.

Bob Barrett: And why should we be screening for MGUS and myeloma?

Sæmundur  
Rögnvaldsson: As I mentioned earlier, we have some studies out now showing that if we treat people at this earlier stage, at a high risk, smolder myeloma stage or asymptomatic myeloma stage, although there is some debate about what is the exact time point there. But most people agree that there are some asymptomatic individuals where treatment is beneficial. And the only way to find these individuals is either randomly, which we don't do very well. As I said, more than 95% of those who get myeloma are not diagnosed at an early stage, or we could do it by screening. So that's the question, sort of, can we do that? And then, is that beneficial? There is, of course, some sort of obvious benefit to diagnose early and treat early, but that might not always materialize. But at least that's sort of the rationale. If we diagnose it early, can we prevent the development of end organ disease?

Sigurður Kristinsson: And also, I think it's important to mention that actually, you should not screen for MGUS. That's what we also write about in the paper. So currently, there is no evidence for screening, so this is why we are doing the iStopMM. So we are asking, is there a benefit to screening for MGUS and multiple myeloma precursors. So it is beneficial for some types of cancer and certainly not all and we have not proven yet that it is beneficial for MGUS.

Bob Barrett: So screening seems to make sense. Why not just start screening tomorrow?

Sæmundur  
Rögnvaldsson:

I think this is a very important question. I mean, there is some sort of theoretical benefit to screening, but this may not always materialize. There are also some important harms that may come from screening. I think about these harms in sort of three parts. Firstly, screening leads to the detection of clinically meaningless disease alongside clinically meaningful disease. This leads to overdiagnosis and more testing and even treatment for people who would never have symptomatic disease. This is what we would call overdiagnosis and overtreatment. This is what happens when we screen, and this can be a very significant harm.

Secondly, screening leads to a diagnosis of a lot of people with this precursor condition who require testing and so on. This is a strain on healthcare systems and incurs cost both for healthcare systems and also for individuals, particularly in some healthcare systems. Now, the third issue is that knowing about a cancer precursor might decrease your quality of life. Knowing that you may have an increased risk of a cancer may sort of increase your or decrease your, what we would call health related quality of life. So your feeling of your sort of sense of wellness, so to speak, is lower.

Sigurður Kristinsson: Yeah, and this is actually what we are studying in the iStopMM study. So we have 80,000 participants. We have 70,000 emails for these participants and we constantly ask them and send them validated questionnaires about their quality of life, about thoughts of illness, about anxiety and depression, and so on. So one of actually the main outcomes of the study is this harm that Sæmundur is talking about. So we really need to understand the significance of these issues in terms of all cancer screening and the literature on that in other types of cancer screening, like breast cancer and cervical cancer screening is very, very limited. So researchers have shown that screening for some cancers increases survival, but that's only one important outcome. There's also the impact of quality of life, which is important.

Bob Barrett: Well, let's go back to that, the iStopMM study. Talk about that study. What is it and what did you come up with?

Sigurður Kristinsson: Right, so the iStopMM study stands for Iceland screens, treats or prevents myeloma. Basically the study is set out to answer the question if we should screen for MGUS. Back in 2016, we invited all Icelanders born 1975 and earlier that were 40 years and older at the time to participate. We invited over 140,000 Icelanders. These are all Icelanders living in Iceland at the time. Amazingly, we got more than 54% of the population to sign informed consent. So over 80,000 people are part of the study. When these individuals were doing blood tests for other reasons unrelated to our study, we got part of that blood sample to send out to The Binding Site in Birmingham, which screened Icelanders for MGUS. So what they returned back was that about 5% of individuals in Iceland 40 years and older, have MGUS.

These people then enter a randomized clinical trial. So we divide them into three equal groups. Arm 1 represents the world that we're living now, where we don't screen and we just go through life as it is. Arms 2 and 3, we call these people in. We do bone marrow, we do imaging, we do blood test, and we follow them for five to seven years. So this is the study, and we need more time to answer the main question, that is, is screening beneficial? But along the way, we have made some progress in redefining the definition of light chain MGUS and we are understanding more and more about the natural history of the disease, about association with other studies, and so on and so forth.

Bob Barrett: Where are you at in this study? Obviously, your recruitment seems to be complete, or do you have any early findings?

Sæmundur Rögnvaldsson: Yeah, so some of the early findings, as Sigurður mentioned, is, of course, a new definition of light chain MGUS and learning more about the disease.

We're also working a lot on improving follow-up strategies for MGUS, which is critical to it being feasible to do screening. We also have presented some data at the American Society of Hematology Congress, both in 2021 and now last year, last December, which actually didn't make it into the paper because it's so new. So it's hot off the press. These findings seem to show that screening leads to early diagnosis of myeloma, about a one year earlier diagnosis of myeloma and related disease, but that those who are in Arm 1 catch up later on. So that sort of at least appears to show that we're not doing that much overdiagnosis.

Secondly, we see that those who are diagnosed with myeloma after screening have much less symptomatic disease, they

have less renal disease and less anemia, and these clinical hallmarks of myeloma and are much less likely to present in an acute manner, where we know that the risk of early mortality in myeloma is the highest.

Thirdly, in that presentation or in that data, we see that at least early on, in the medium term, knowing about your MGUS status does not significantly affect people's levels of depression, anxiety, or satisfaction with life, and that's on average. But it's important to take these findings with some grain of salt because we don't know whether this sort of translates into improved survival later on. These psychological benefits are in the setting of this study, where people enter very sort of very systematic follow-up and also all care is free of charge. So that's very important to take into account there.

Bob Barrett: Finally, you both seem to be really enthusiastic about this study and this paper. Is there anything else you'd like to share on the topic?

Sæmundur Rögnauldsson: Well, I think our conclusion in the paper in *Clinical Chemistry*, it's very important to share that conclusion, because to date, we don't have the data to start screening. I think it's important that we're clear on that. There is promise in screening, but we need more data, and we need more time to know whether we should do it. It's an incredibly big intervention into just society to start screening for MGUS because MGUS is so common. So it's very important to be sure that we're doing the right thing when we start it. There are some clinical scenarios where screening is appropriate, families with loads of myeloma and so on, but sort of population-based screening, it's not time for that yet, but we're working on it.

Bob Barrett: That was Dr. Sæmundur Rögnauldsson and Dr. Sigurður Kristinsson from the University of Iceland. They wrote a review article discussing multiple myeloma screening in the January 2024 issue of *Clinical Chemistry*, and they've been our guests in this podcast on that topic. I'm Bob Barrett. Thanks for listening.