Screening for monoclonal gammopathy of undetermined significance: A population-based randomized clinical trial

State of the art

Four percent of individuals over the age of 50 years have a monoclonal gammopathy, which is associated with a 1-2% annual risk of malignant transformation and reduced overall survival. Currently we are unaware of the underlying causes of monoclonal gammopathies, we cannot predict which individuals with precursor states will progress to full-blown malignancy, there is no evidence from prospective studies to guide clinicians and patients for the optimal follow-up, the impact of hereditary factors, genetics, imaging, and other molecular markers on transformation is unknown, nor do we have scientific evidence for screening. Thus all individuals with precursor states are identified out of pure coincidence because of another unrelated sickness. Our proposed study will be the first screening study on monoclonal gammopathy of undetermined significance (MGUS) in a whole nation and the first prospective randomized clinical trial with the aim of evaluating the impact of screening and the best follow-up strategy for MGUS.

Monoclonal gammopathies are disorders characterized by a spike in a homogeneous immunoglobulin (the M-protein) in serum (SPEP) or urine (UPEP) protein electrophoresis, or an abnormal kappa to lambda ratio on free light chain (FLC) analyses, and can be detected by a simple test, and arise from the proliferation of an abnormal clone of a single plasma cell precursor.[1] Multiple myeloma (MM) is the archetype of a malignant monoclonal plasma cell disorder. Once it was observed that a substantial proportion of benign gammopathies develop into MM, the now universally accepted term *monoclonal gammopathy of undetermined significance (MGUS)* was introduced to describe the disorder.[2]

MM is a neoplasm characterized by the proliferation and accumulation of malignant plasma cells in the bone marrow that lead to the overproduction of M-protein in the serum or urine. In the Western world, the annual age-adjusted incidence for MM is 4.8 to 8 per 100,000.[3] The median age at diagnosis is approximately 70 years.[4] A total of 40 individuals are diagnosed with MM or related lymphoproliferative disorder every year, thus after 5 years of follow-up in our study approximately 200 patients will have progressed.

Myeloma related end-organ or tissue impairment resulting from this disorder include the classic "CRAB" symptoms of hypercalcemia, renal insufficiency, anemia, and lytic bone lesions and the less classical symptoms of hyperviscosity, amyloidosis, and recurrent bacterial infections.[5] In addition, in the recently updated diagnostic criteria, MM now includes biomarkers and imaging in the diagnostic criteria.[1] MM remains incurable, however, in recent years, several new therapeutic agents with novel mechanisms of action have been approved for MM such as immunomodulatory agents and proteasome inhibitors, and few cancers have experienced more rapid treatment development in recent years.[6] This has led to a significant improvement in survival of MM in the general population,[4,7-10] with the current median overall survival of more than 6 years (compared to 2-3 years in the 1990s).[11,12] **Now, the evidence is emerging to consider population screening to identify subjects at risk for MM and follow-up studies to start treatment in an earlier phase of the disease.**

MGUS denotes the presence of an M-protein on electrophoresis in patients without evidence of MM, Waldenström macroglobulinemia, amyloidosis or other lymphoproliferative diseases. MGUS is characterized by the following: a serum M-protein concentration less than 30 g/L; less than 10% clonal plasma cells in the bone marrow; little or no M-protein in the urine; absence of the CRAB criteria.[1] Light-chain MGUS (LC-MGUS) is recently described and is based on FLC analysis, and is defined as a pathological FLC ratio (outside reference range 0.26-1.65) in combination with an increased concentration of the light-chain concerned (f-kappa>19.4 or f-lambda >26.3), without evidence of MM, lymphoproliferative diseases, amyloidosis or classical MGUS.[13]

There are 3 types of MGUS with distinct natural histories: non-IgM-(IgG or IgA)-MGUS, IgM-MGUS and LC-MGUS.[13,14] While IgG and IgA- and LC-MGUS typically progress to MM or develop light-chain-amyloidosis, IgM-MGUS cases more often progress to lymphomas.

The prevalence of MGUS is highly dependent on age and is reported to be found in approximately 5-10% of those older than 70 years which makes it a very attractive condition to study in order to understand plasma cell diseases.[15,16] Data from the Mayo Clinic suggests that MGUS is present in about 4.2% of the general Caucasian population aged 50 years and older and is predominantly diagnosed incidentally.[13,15] We recently performed a large, population-based screening cohort study,[17] and included 5,764 Icelanders born

1907-1934 in Iceland. We found the prevalence of MGUS to be 5.3% and LC-MGUS was 1%, thus we confirm that Iceland has a similar prevalence as other western countries, making it suitable for nationwide studies, especially since its population is approximately 340,000 with few people emigrating and a government-maintained health care regardless of socioeconomic status. **The results can be used to assess whether population wide screening is beneficial on a European level but also to determine the disease mechanisms.**

Similar to MGUS, smoldering MM is a precursor condition to MM and is defined by the clinical parameters of M-protein ≥ 30 g/L or bone marrow plasma cells ≥ 10%.[1] We recently found, based on all smoldering MM patients diagnosed in Sweden 2008-2011, that smoldering MM accounts for 14.4% of all MMs the age-standardized incidence of smoldering MM was 0.44 cases per 100,000 persons.[18] Smoldering MM is therefore included in our studies.

Etiology

The etiology of MGUS is unknown. We have shown that there is a familial aggregation in MGUS and related diseases.[19-24] Additionally, differences in racial disparity patterns have been observed in MGUS (with the risk of Africans and African-Americans being approximately twice as that if whites), suggesting genetic or environmental causes.[25,26] The genetic basis of inherited MM and MGUS susceptibility is incompletely understood. Recent genome-wide association studies have identified eight common sequence variants that associate with MM, and account for an estimated 13% of the familial risk.[27-29] We recently performed a study and identified a new MM risk locus at the ELL2 gene, which encodes a stoichiometrically limiting component of the super-elongation complex that drives secretory-specific immunoglobulin mRNA production and transcriptional regulation in plasma cells.[30] However, these known variants account for a minority of MM and MGUS cases and further work is needed. In addition, the clinical impact of these variants on progression from MGUS to MM is completely unknown. Interestingly, we found that the MM risk allele at ELL2 also associated with reduced levels of immunoglobulin A and G in healthy subjects and, with an increased risk of bacterial meningitis.[30] There is further epidemiological evidence for an association between chronic antigen stimulation and risk of MM, MGUS and lymphoproliferative diseases, and individuals with prior history of infections and autoimmune diseases have been shown to be at increased risk of these disorders.[31-35] How prior history of infections and autoimmune disease affects progression to MM is not known and needs to be studied. Additionally, the interaction between environmental and genetic factors is not known and could be of relevance. One of the challenges in identifying risk factors has been limited number of MGUS individuals, lack of information on genetic factors, and the relationship and possible synergism between hereditary and environmental factors. **Our plan is to evaluate the impact of germline genetic factors in this disease, which has never been done MM or related diseases.**

"Undetermined" significance?

Since the term "undetermined significance" was introduced,[2] we and others have shown, in a number of clinical and screening studies that individuals with MGUS have not only an increased risk of progression to MM, lymphoproliferative diseases, and amyloidosis, but also other diseases, such as fractures[36-41], infections[42,43], thrombosis[44,45], non-lymphoproliferative malignancies[46] and inferior survival compared to non-MGUS individuals.[47-51] Additionally, we found increased risk of death due to malignant and non-malignant disorders.[52] Therefore, we should probably rethink the term "undetermined significance", as a lot of data have emerged since it was introduced almost 40 years ago, indicating the clinical significance of MGUS. **It has become clear in recent years that MGUS is of major significance and its impact on a national level needs to be established in a population-based prospective study. Our plan is to provide the evidence for the significance of MGUS on a population-based level that will have important consequences in other counties as well.**

Progression of precursor states

The big research question in precursor states is to identify those that progress and might benefit from intervention. Current risk models for progression include different markers, and are thus not integrated with one another, have limited direct correlation to biology, and cannot reliably predict progression in patients with MGUS.

The risk of progression in smoldering MM is estimated to be an average of 10% annually for the first 5 years following diagnosis (51% risk of progression at 5 years), then decreasing to 3% annually for the next 5 years and 1% annually for the following 10 years.[53]

Two large independent studies indicate that MGUS always precedes MM.[54,55] The average risk of progression is estimated to be 1.5% per year.[47,56,57] However, there is considerable variation in the risk of

progression, and differentiating low-risk patients, who may not need further follow-up, from high-risk patients, who may warrant close monitoring or enrolment in early intervention studies, is a challenge. Models have been published for risk stratification of MGUS patients.[56,58] Risk factors included in a Mayo Clinic model are non-IgG isotype, M-protein concentration ≥15 g/L, and an abnormal serum FLC ratio.[56] Risk factors in the Spanish study group (PETHEMA) model are based on multiparametric flow cytometry and include the presence of ≥95% abnormal plasma cells and aneuploidy.[58] **Similarly, two prognostic scores exist for smoldering MM, however a recent study found almost 30% discordance between the models, emphasising the need for prospectively validated models in MGUS or smoldering MM.[59]**

Importantly, the optimal imaging technique is not established and modern radiological examinations (such as CT) have not been evaluated in large prospective studies. The current standard for skeletal imaging in individuals with monoclonal gammopathies is the conventional skeletal X-ray. It has some major limitations, including limited sensitivity and specificity, and it is time consuming for patients and observers.[60] CT scans have been shown to be superior however there are some concerns regarding radiation exposure, particularly in patients with MGUS. Recently, whole body low-dose multidetector row-CT have been studied and have been shown to detect small lesions, are much faster than standard radiology, can show soft tissue disease and has higher sensitivity and specificity than conventional X-ray.[60-62] It has been shown to be more sensitive than MRI to detect small lesions.[63] MRI has some benefits, for example to no radiation and is able detect marrow infiltration, however this is not of major importance as bone marrow biopsies are taken and in addition it is more time consuming. The radiation exposure using low-dose CT is only 1.7 times more than standard X-ray, whereas conventional whole body CT is 10.6 times higher radiation, with very good quality.[64] **Therefore, low-dose CT could be the optimal radiological examination for MGUS individuals, and this needs to be addressed in a prospective study.**

At this time there is no way to prospectively determine which patients will follow which course at the time of initial diagnosis. There are no prospective studies to guide management of patients with MGUS, however expert opinions suggest, depending on the individual patient's clinical risk score, life-long monitoring of MGUS individuals to detect progression to MM or related disorders.[65,66] The impact of annual monitoring on the outcome of patients who eventually develop MM or related diseases is unclear. **There is a great unmet need for a prospective trial to evaluate the most optimal follow-up strategy that is effective, and minimizes the need for unnecessary work-up. Our plan is to perform a nationwide screening study, and consequently a randomized clinical trial (RCT) to evaluate the optimal follow-up strategy.**

To evaluate the impact of MGUS follow-up, we recently performed a large population-based study on more than 14,000 MM patients diagnosed in Sweden 1976-2005, with follow-up through 2007.[67] We compared survival in those with a known prior MGUS compared to those without prior knowledge. We found a total of 394 MM patients had previously been diagnosed with MGUS and MM patients with prior knowledge of MGUS had significantly 14% decreased risk of death (HR=0.86; 95% CI 0.77- 0.96) than MM patients without prior knowledge of MGUS (Figure). Results were similar when restricted to patients diagnosed with MM after 1996, with MM patients with prior knowledge of MGUS having significantly (HR=0.81; 95% CI 0.70-0.93) better survival than MM patients without prior knowledge of MGUS. Our findings are consistent with a prior smaller study including 116 MM patients seen at the Mayo Clinic between 1973 and 2004 showing that low-risk MGUS patients are more often diagnosed with serious complications compared to high-risk MGUS patients.[68] Also a similar finding was observed in another large cohort study from USA.[69] Interestingly, in our study, we found that among MM patients with prior knowledge of MGUS, low M-protein concentration (<5 g/L) at MGUS diagnosis (low-risk) was associated with poorer MM survival (HR, 1.86; 95% CI, 1.13-3.04). This may be reflective of current expert opinion suggesting less frequent monitoring of MGUS patients with lower M-protein concentrations (low-risk patients). We speculate that the reason for the prolonged survival observed in our study, most likely reflects the fact that MGUS patients are evaluated more often for signs of MM progression and may be diagnosed and started on anti-myeloma therapy at an earlier stage. **This argues for early treatment approaches in MM,[70] and raises the question whether systematic screening for MGUS should be initiated.** Alternatively, those with more aggressive disease may have a shorter duration of MGUS and are less likely to be diagnosed and captured during the MGUS state. This is a very important issue, especially in the current times when there is a paradigm change in the way we think of these disease and its management, with novel drugs proving to benefit even the asymptomatic patients (see below). This can only be properly analyzed in a prospective study like our proposed study.[71]

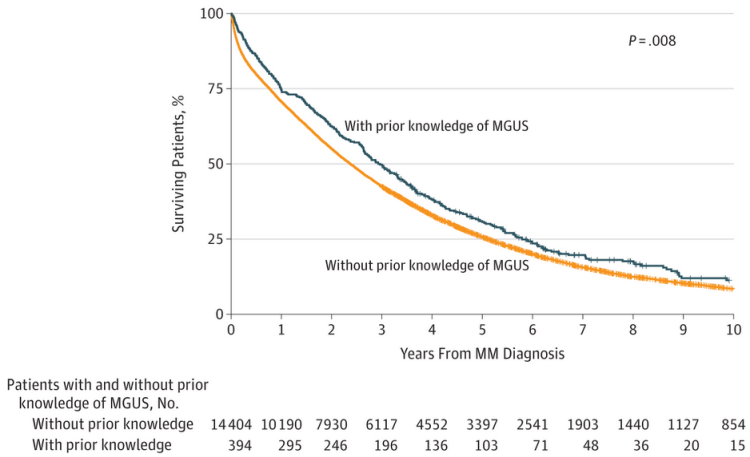

Figure. Survival among MM patients with and without prior knowledge of MGUS

Treatment of multiple myeloma precursor states

As discussed above, it has become relevant to consider preventive management of patients with smoldering MM and possibly high-risk MGUS.[72] While earlier studies using older and less effective treatment options did not demonstrate a survival benefit from treating smoldering MM,[73-75] recent prospective RCT using lenalidomide and dexamethasone versus no treatment in high-risk smoldering MM showed that the risk of progression to MM was significantly lower and importantly, overall survival was significantly longer in lenalidomide-dexamethasone treated patients.[70] Several RCT are ongoing validating this important finding that suggests a paradigm change in the management of smoldering MM. Very recently, the NCI group published a study on 12 smoldering MM patients with carfilzomib, lenalidomide and dexamethasone.[76] This trial showed that all patients reached minimal residual disease negativity, suggesting that this might be the future reference for standard of care. Very few studies have been performed to treat patients with MGUS, which is logical as most MGUS individuals will not progress. One study group, however, treated 26 MGUS individuals with oral curcumin, the most active component of the commonly used Indian spice turmeric, and observed a decrease in M-protein.[77] Interestingly, a recent cohort study, including 2,003 MGUS patients with diabetes mellitus, found that those that were on metformin (for diabetes mellitus) had a significantly lower risk of MM transformation than non-metformin users.[78]

It is very likely that in the coming years, with more potent therapies entering the therapeutic arsenal with fewer side effects, treatment of precursor states will be shown to improve survival and QoL in smoldering MM and MGUS patients. These individuals are, by definition, asymptomatic and therefore they will be diagnosed either as a coincidence due to work-up for an unrelated medical condition or as a part of a screening program. **Given that the literature is growing and favouring treatment of high-risk asymptomatic patients, one major challenge is the fact that most of these patients will remain undiagnosed.** Currently most expert guidelines do not recommend treating high risk smoldering MM, however we envision that in the near future, there will be a paradigm change with regards to management of these patients. As soon as another RCT shows difference in overall survival favouring active treatment against therapeutic abstinence, there will be a major shift in treatment strategies throughout the world. Many authorities consider that early treatment is the way to go if we are aiming to cure MM.[79] **With that in mind, our ambitious program will identify all these patients in the Icelandic population, and can therefore capture a malignant transformation earlier and thus being able to offer treatment and hopefully cure for these patients as the evidence emerges.** We predict, based on ongoing studies and recent results,[70,76] that these advances will probably emerge within the next few years.

Screening

Screening for a disease is not uncontroversial.[80-82] Several aspects need to be taken into account, such as clinical benefit of early detection, potential harm, and cost. These special circumstances to invite individuals without knowledge of a disease in question for screening can have desirable and undesirable consequences. One important topic is the anxiety and distress associated with the knowledge of a precursor disease. This has not been studied at all in MGUS and the literature on this issue is very limited in screening for cancer in general, however there are studies on colorectal, prostate, ovarian, and breast cancer that suggest that the burden of anxiety and QoL are limited but not negligible, mainly due to overdiagnosis and treatment related

issues.[83-90] Weighing the balance between the benefits and harms of MGUS screening is essential for decision making regarding screening at both the individual and the policy level.

Wilson and Jungner attempted to define screening criteria to guide the selection of conditions that would be suitable for screening.[91] These need to be carefully addressed when discussing screening programs and are listed below, with comments regarding MGUS:

1. The condition sought should be an important health problem.
The impact of MGUS, MM, lymphoproliferative diseases and amyloidosis is a very important health problem.

2. There should be an accepted treatment for patients with recognized disease.
Currently there are several accepted and highly effective treatment options for MM, lymphoproliferative diseases and amyloidosis.

3. Facilities for diagnosis and treatment should be available.
These are available for MGUS and related diseases.

4. There should be a recognizable latent or early symptomatic stage.
MGUS and smoldering MM are known and well-defined precursor states.

5. There should be a suitable test or examination.
Electrophoresis and FLC analyses are easy blood test to perform.

6. The test should be acceptable to the population.
A simple blood test is acceptable.

7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
This is known in MGUS.

8. There should be an agreed policy on whom to treat as patients.
There is an agreed policy, however this is a moving target and the trend is to treat earlier stages of disease.

9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
The cost for electrophoresis and FLC is not high, and cost can be kept low by including and collaborating with other national screening programs.

10. Case-finding should be a continuing process and not a "once and for all" project.
This is true for MGUS.

It is clear, as summarized above, that MGUS is a very common precursor conditions and most studies on work-up, follow-up, and monitoring are based on retrospective case series. As suggested by the Dr. Robert Kyle, who originally termed the condition and is the pioneer in the work of monoclonal gammopathies together with Dr Vincent Rajkumar: "*We need prospective studies to address the value of follow-up in MGUS and the optimal approach to such follow-up. The risk-adapted approach is a compromise that ensures that scarce resources are focused on the patients most likely to benefit. We also need studies to address the question of the possible merits of screening for the presence of MGUS in a normal, older population*."[71]

Objectives
The overall objective of this study is to provide evidence for a paradigm change in the management of individuals with monoclonal gammopathies by evaluating the impact of screening for MGUS on overall survival and mortality in MM, lymphoproliferative diseases, and amyloidosis, and establish the optimal follow-up strategy. We propose to invite all individuals born 1975 or earlier in Iceland (approximately 140,000 individuals) to participate in a nationwide screening study for MGUS and smoldering MM and invite those that are diagnosed with MGUS and LC-MGUS to be included in a RCT to evaluate the impact of

screening and the optimal follow-up strategy. Also we plan to use an innovative approach by improving risk models for progression. Hopefully our study will lead to a theoretical change in how risk models are conducted with inclusion of genetic, imaging, environmental, and biological factors. Also the impact of early diagnosis and treatment of smoldering MM and MM in a whole population is a very ambitious and challenging goal.

Specific aims

1. To evaluate whether overall survival is improved by screening for MGUS.
2. To evaluate whether cause-specific survival is improved in screened MGUS individuals.
3. To evaluate the effect of screening for MGUS on quality of life, depression, and anxiety.
4. To evaluate the cost-effectiveness of screening for MGUS.
5. To evaluate the optimal follow-up strategy for individuals with MGUS-based on risk adapted criteria.
6. To evaluate the impact of screening for smoldering MM in a population.
7. To evaluate the effect of early treatment in a screened population of MM, lymphoproliferative diseases, and amyloidosis in a whole nation.
8. To identify the optimal approach to radiological and bone marrow examinations in MGUS.
9. To identify novel genetic variants as risk factors for development and evaluate the impact of germline variants on progression
10. To integrate clinical factors, protein markers (including immunoglobulin free light-chains) and immunophenotyping by flow cytometry with molecular profiles (including gene expression profiling), and the event of disease progression.

Originality

This study is the first screening study on MGUS in a whole nation and the first prospective randomized clinical trial with the aim of evaluating the impact of screening and the best follow-up strategy for MGUS. We present a well-designed population-based study screening study, utilizing in a simple, effective and a smart way the fact that individuals are having their blood drawn for various reasons unrelated to MGUS. By using this approach we will be able to obtain blood samples from the large majority of individuals in Iceland (approximately 300 individuals per day during the first months and decreasing to approximately 150 per day thereafter based on numbers from the Department of Clinical biochemistry) thus ensuring a very fast recruitment rate, without the need for infrastructure for blood sampling, reception, administrative and personnel, as the individuals are doing the blood test for reasons unrelated to MGUS, regardless of the current study. By obtaining informed consent electronically the unique Icelandic personal identification number will be linked at regular intervals to the software at the biochemical departments and when a blood sample from individuals agreeing to participate is drawn, it will be flagged and extra sample saved for the current study.

By using the unique government maintained personal identification codes (IDs) we can invite every single resident of Iceland born 1975 and earlier to participate. These IDs can also be used to identify all subsequent cancer diagnosis and other diseases (based on ICD-codes) for prior and subsequent disorders and information on vital status with almost 100% accuracy (as explained below).

We propose to use a simple, yet safe electronic informed consent form. By collaborating with the Icelandic Cancer Society we will be able to use the infrastructure already present for other screening program to contact participants, send out information letters, routines for check-ups according to the current protocol. Importantly, the Cancer Society has more than 80% participation rate in different screening programs.

It is important to note that we are not proposing to start a screening program for MGUS. **Rather we are evaluating the hypothesis,** based on emerging data, that screening for MGUS is beneficial by leading with a good example and provide the best evidence for screening, by conducting a RCT. Only individuals that do not get tested during the first 2 years will be asked to donate a sample especially for the study. We estimate that only a minority of participants will not do a blood sample during the screening phase of the study (3 years), thus minimizing this need and lower the cost and need for extensive infrastructure.

Since there is no evidence based on RCT or prospective studies, for best follow-up of MGUS, regardless of the results from the screening part of the study, we will still be able to provide evidence for the optimal follow-up strategy and the natural history of the disease, and identify risk factors for progression. **Our large study, including the screening and RCT part, together with unique infrastructure and possibilities for a complete surveillance, as well as extensive genetic, imaging, molecular, and bone marrow studies, will provide excellent opportunities for several spin-off projects on the biology of MGUS.**

An important part of the study is including QoL assessments, which will have relevance outside the scope of monoclonal gammopathies and will give important scientific and clinical information regarding screening programs in general. Also this applies to cost-effectiveness which will be a major part of the interpretations of the overall findings and its generalizability.

Impact
The findings from this study will have great clinical, scientific and health policy-making impact on a global scale, partly due to the fact that MGUS is so common (more than 4% of people over the age of 50 years), and that there is no data from prospective clinical studies to guide management of these individuals. Also, if screening for MGUS is found to be effective, it will have major impact on health care systems and screening programs throughout the world, as this will impact the standard of care for future MGUS management. This will in turn affect individuals with MGUS and their family members, and guide future management of this common condition, and hopefully lead to the optimal follow-up strategy and the best use of resources in health care systems. Beyond MGUS the analyses on QoL, can potentially have implications for the harms of screening program, which is of major relevance in the screening literature and interpretations of effectiveness. If found effective, screening and consequently early diagnosis of MM, smoldering MM, lymphoproliferative diseases and amyloidosis will give unique opportunity for early treatment strategies which will have the potential of curing these diseases.[92]

Methodology

The study can be divided into two themes and several subthemes:

A. Screening and a randomized clinical trial
i. Nationwide screening for MGUS
ii. Nationwide prospective RCT for optimal follow-up strategy
iii. Follow-up from the RCT and screening study on incidence of cancer, subsequent diseases, and vital status.

B: Progression
i. Population-based prospective natural history study of MGUS and smoldering MM based on screening
ii. Integrating germline genetic variants, molecular factors, imaging, and clinical factors in risk assessment for progression

Study population for parts A and B
We will invite all individuals living in Iceland that are born 1975 and earlier to participate in the screening part of the study. From the Register Iceland (Þjóðskrá Íslands) we will obtain a complete list of these individuals, including full name, unique IDs and home address. Currently, more than of 140,000 individuals living in Iceland are born 1975 an earlier. All these individuals will be invited to participate by a letter sent to their home address. This letter will contain a brochure with information on MGUS, the study design, participation, and rights. Also it will include two ways of informed consent:
1. A letter with information of rights and duties of participants, which can be signed and posted via mail (free of charge for participants-cost covered by the project). This will be sent to the study coordinator and registered in an electronic database.
2. Electronic informed consent. Participants are also given the opportunity to log on to the study´s homepage: www.MGUS.is and log on with their identifier and a unique password for each participant or to use the government maintained e-certificate (see https://www.island.is/en/icekey-e---certificate/about-icekey/ for details on e-certificates). The participant will then get the opportunity to confirm consent or "I wich not to participate in the research".

We estimate, based on other nationwide studies performed in Iceland and Cancer screening programs that 80% will accept participation in the screening part of the study.[17]

Computerized database
A database with each individual, including name, ID, and home address will be built. Individuals who agree to participate will be registered in the electronic database including the ID. Individuals who do not want to participate will not be registered or contacted further.

Pilot Project
A pilot project to test the information material, the electronic informed consent, stress tests for the homepage, and recruitment strategies will be done. This will only include people from Akranes, a town with approximately 3,000 individuals 40 years or older, and will be performed in late September/early October.

Registries
The nationwide Icelandic *Cancer Registry*, which was established in 1951 has more than 99% completeness and over 96% diagnostic accuracy.[93] Information on prior and subsequent MM, lymphoproliferative diseases and other malignancies as well as prior MGUS will be obtained by cross linking with participant´s ID list. The Icelandic *Patient Registry*, captures ICD codes throughout Iceland, including all in- and outpatient care. *Register Iceland* includes a complete list of all residents of Iceland with dates of birth, dates of death (updated weekly).
Cause of Death Registry, digitally registered since 1971, based on death certificates and coded according to ICD-10 since 1996. It is a nationwide register that registers all deaths with primary cause of death and all underlying causes for all residents of Iceland.

Specific risk groups
Information on family history will be included in the study project and family tree information obtained from genealogy database at Landspitali University Hospital. This will enable stratified analyses on screening particular risk groups, as MGUS and MM have been shown to aggregate within families.[19,24] Also autoimmune disease has been described as a risk factor for MGUS and MM[35], and information on autoimmunity and other diseases, will be obtained from the Patient Registry. Iceland is predominantly a Caucasian population and thus we cannot compare the impact of screening among different races, which is a limitation, as black race is a known risk factor for MGUS and MM.[10,25,94] Overall, the inclusion of specific risk groups is feasible due to the unique infrastructure in Iceland with cross-linkage of personal IDs to different official registries with almost 100% completeness. This will allow us to perform a state of the art scientific approach that is not possible in other countries due to large number, lack of infrastructure, and high cost.

Blood sampling
Participants will not be contacted for blood sampling in this study (see flowchart in annex). Rather we will use an innovative approach by taking advantage of the fact that most people that are 40 years or older, do a blood test for various reasons during a 3 year period (for example just at the Landspitali during the first 8 months of this year, blood has been drawn from 37,404 (35%) individuals 50 years and older). We will cross-link the ID list from all participants in the computerized database to the database of all major laboratories in Iceland, which covers approximately 90% of all blood sampling in Iceland, including the Reykjavik area and surrounding towns, Akureyri, Akranes, Ísafjörður, and Selfoss. A software will be designed to link these two sources (1. participants and 2. people donating blood samples at different labs) so that participants in the study donating blood will be flagged and sample for the study obtained. When a participant does a blood sampling for any reason, the software will be programmed to flag the sample. Then 1 mL of serum aliquot will be separated from the serum to a separate test tube belonging to the study, which will be marked with a bar-code unique for this individual. The samples serum will then be stored at 4°C. At regular individuals, a package including 200 samples, anonymously marked with a unique barcode, without any identification, will be shipped to Binding site, in Birmingham UK, for analyses (see below). To prevent repeated measurements from the same individual, the database will be updated when an individual has already donated blood for the study.

Electrophoresis and free light chain analyses
SPEP, immunofixation, and FLC analyses from all participants will be performed at Binding Site laboratory that will fund the analyses (see Letter of Support). The Binding Site Group Ltd (TBS) is a specialist protein company which is committed to the research, development, manufacture and distribution of innovative immunodiagnostic assays for the global laboratory market. TBS has state-of-the art and fully equipped laboratories for assay development, production and validation. For these analyses 1 mL serum from each patient will be shipped from Iceland to UK. We will evaluate for a) presence or absence of an M-protein, b) concentration of the M-protein in g/L, c) isotype of the M-protein (IgG, IgA, or IgM), d) presence or absence of an abnormal kappa:lambda ratio, and e) kappa:lambda ratio. Once the analyses have been performed, the

results from these analyses will be sent to the study coordinator in Iceland. Individuals found to have MGUS or LC-MGUS will be included for further studies on progression and invited to the RCT (see below).

A. Screening and a randomized clinical trial

Randomized clinical trial
Participants found to have evidence of MGUS (N=2,560 based on estimate of 3.2%) or LC-MGUS (N=800 based on 1% estimate) will be randomized to one of three arms of the study (flowchart in annex). Arm 1 and 3 will be invited for a medical work-up. Individuals randomized to Arm 2 of the RCT, undergoing routine clinical care will only be registered and not worked up further. Individuals in Arm 2 of the randomized clinical trial will be informed about the findings of MGUS, i.e. at the finding of inferior outcome for Arm 2 during interim analysis, these will be informed that they have MGUS and offered to be randomized into Arm 1 and Arm3.

Inclusion criteria: All individuals, born 1975 or earlier, with registered address in Iceland on November 1st, 2016 will be offered to participate in the study.

Exclusion criteria: Individuals with prior MM, lymphoproliferative diseases and amyloidosis are not eligible for the study. All individuals with M-protein>30 g/L or involved:uninvolved serum FLC ratio ≥100 be contacted and followed in order not to miss underlying MM and therefore not randomized into Arms 1-3. Individuals with prior history of MGUS will be offered to be randomized into either Arm 1 or Arm 3, but not be used for comparison with Arm 2.

Arm 1: Follow the current recommendation from an expert group of the International myeloma working group (IMWG).[65] This includes a complete blood count, serum creatinine and calcium measurement in low risk patients without CRAB criteria. Patients will be followed with SPEP in 6 months, and if stable can be followed every 2–3 years or when symptoms suggestive of a malignancy arise. Intermediate and high risk MGUS patients will undergo a BM aspirate and biopsy, including conventional cytogenetics and FISH. A CT scan of the abdomen will be done in the presence of an IgM M-protein and plain skeletal X-ray in others. If the results of these tests are satisfactory, patients will be followed with SPEP and FLC and a complete blood count in 6 months and then annually.

Arm 2: Routine clinical care only, and therefore no further work-up.

Arm 3: Careful medical history and physical examination. A complete blood count, serum creatinine, calcium, cardiac markers and liver function tests will be measured. A bone marrow evaluation and low-dose skeletal CT/abdominal CT will be performed in all patients. All patients will be followed at least annually with medical history, clinical examination, laboratory analyses (complete blood count, electrolytes, SPEPP and FLC) and lower threshold for bone marrow at signs of progression.

Follow-up
All three treatment arms will be followed for progression to MM and lymphoproliferative disorders, by cross linking to the Cancer Registry and for other diseases by cross-linking to the Patient Registry. Information on all subsequent cancer diagnosis and other diseases (based on ICD-codes), both prior and subsequent to inclusion and information on vital status will be gathered with almost 100% accuracy.

All personnel involved in the RCT will attend a course in good clinical practise (GCP) and need to fulfil the GCP standards for serving as investigator.

Outcomes measures in RCT
The primary outcome of the RCT and screening is overall survival. Secondary outcomes include cause-specific survival (in MM, lymphoproliferative diseases and amyloidosis). In addition to following MGUS patients within the RCT, it is of importance to follow non-MGUS individuals. This is a novel approach and has not been studied in MM or related disease before and is highly important to identify those that are diagnosed with MM, PL or amyloidosis without prior MGUS or those with short MGUS duration. All participants in the screening part of the study (individuals in all three arms of the RCT together with those without MGUS) will be followed for all incidence cancer diagnoses by cross linking to the Cancer Registry.[93] Data from the study population will be cross linked to the Cancer Registry regularly (2 times per

year) and thus all subsequent cancer diagnoses registered. Also, it will be cross-linked to the Patient Register to obtain information on prior autoimmune disease and all subsequent non-malignant diseases.

Data on vital status will be obtained at regular intervals (every three months) and obtained from Registers Iceland, which includes vital status information on all residents of Iceland with 100% completeness. Information on survival in selected cancers will be obtained by using date of cancer diagnosis and date of death, or date at the time of analyses.

If a patient is diagnosed with MM, lymphoproliferative diseases, or amyloidosis, during follow-up, the patients will be referred to a hematologist for management. Also, as the PI for this proposal is a member of the steering committee of the Nordic Myeloma Study Group (NMSG), who execute trials in MM, for example with early intervention in smoldering MM. Thus progressing individuals will hopefully be offered inclusion in such a trial with another informed consent form. Patients that progress, will exit the RCT, but will still be included in the screening part of the study to estimate survival in MM, lymphoproliferative diseases and amyloidosis between the 3 arms of the study.

Assessments of quality of life, anxiety and depression and cost-effectiveness

An important part of all screening studies and RCTs is the effect of screening and follow-up on QoL. The literature on QoL in MGUS is very sparse; in fact we are not aware of any studies on the subject in the literature. To evaluate whether knowledge of MGUS is associated with anxiety about progression to MM, lymphoproliferative diseases or amyloidosis and how QoL is in MGUS patients in general compared to non-MGUS individuals, we plan to examine QoL by using the Patient Health Questionnaire (PHQ-9)[95], Generalized Anxiety Disorder (GAD-7)[96], and Satisfaction with Life Scale (SWLS)[97]. The PHQ-9 is an instrument for screening, diagnosing, monitoring and measuring depression and scores each of the 9 DSM-IV criteria as "0" (not at all) to "3" (nearly every day). The GAD-7 is a self-reported questionnaire for screening and severity measuring of generalized anxiety disorder. The SWLS is a short 5-item instrument designed to measure global cognitive judgments of satisfaction with one's life.

QoL assessments will be performed electronically after informed consent has been signed. Both test will be found on the study web page www.MGUS.is, thus obtaining information before study participants know they have MGUS. Subsequently, QoL assessments will be performed every year in individuals in arms 1 and 3 (active follow-up) and a random sample of other 5000 individuals. By using this approach, a good estimate of QoL changes can be detected, both by internal comparison, i.e. QoL results compared in persons before and after they received the diagnosis, and by comparing changes over time in MGUS versus others. Calculations of cost-effectiveness will be performed in collaboration with collaboration with the Department of economy at the University of Iceland and will include standard estimates.

Data monitoring committee

An independent data monitoring committee (DMC) will be established for the RCT part of the study, for evaluating risk/benefit when possible and evaluating the efficacy of the treatment at the time of interim analysis in study. The primary purpose of this DMC is to ensure the safety of the subjects in this study by monitoring safety data collected in the clinical program and to evaluate the interim safety and efficacy data and to provide recommendations to the study team. The DMC will make recommendations concerning the conduct of the study. The DMC will be comprised of two clinicians and one statistician.

Interim analyses

The first interim analysis will be performed after 500 subjects have been followed for at least 6 months. This is anticipated to be approximately 7-8 months after first subject has been randomized (see working plan below). The purpose of this interim analysis is to have a comprehensive evaluation of safety, because there are limited safety data for screening for MGUS. The second interim analysis will be performed when 100 events (deaths) have occurred. This is anticipated to be approximately 11-12 months after the first subject has been randomized. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. In addition to the above described interim analyses, biannual interim analyses will be performed for safety, and to evaluate of the primary objective of the study has been reached. The DMC will carefully review the interim results for recommendation of early termination due to overwhelming efficacy or lack of efficacy.

In case Arm 2 has worse outcome, individuals in Arm 2 will be unblinded. These individual will then be invited for a medial appointment and informed about the findings. They will then be invited to continue participation in the trial and consequently randomized to the remaining 2 arms of the study. This is to evaluate the most optimal follow-up strategy for MGUS. Those refusing further participation will be referred

to a hematologist for further work-up and follow-up. In case the study objectives are reached, the RCT part will be terminated and individuals informed about their MGUS.

Data monitoring will be done by an independent company, who have a long lasting experience with monitoring clinical trials.

Ethical consideration

One of the main ethical issues is the fact that individuals randomized to Arm 2 of the study will not get information on their MGUS and will undergo routine clinical care and thus not be worked up or followed beyond that what normally happens in the population. This is in our mind ethically defendable for several reasons. First, approval for this study will be obtained from the Ethical Committee in Iceland. Second, we already know that 4.2% of the population over the age of 50 years have MGUS and these are not being captured or evaluated. Third, we will not randomize individuals with M-protein>30 g/L or involved:uninvolved serum FLC ratio ≥100 in order not to miss underlying MM. Fourth, we have pre-planned several interim analyses to detect any differences in outcome and will terminate the study and unblind individuals in Arm 2 in case of inferior efficacy (after recommendation from independent DCM). Fifth, individuals will be thoroughly informed about the study design and can whenever they want decide to stop participation. Sixth, individuals in the RCT will still be able and encouraged to seek medical help in cases of sign/symptoms of any serious illness and can be diagnosed with MM, MGUS or any other disorder as other people in the general population.

Statistical analyses

Prevalence of MGUS and LC-MGUS, with 95% confidence intervals (CIs), will be estimated with a binomial test. Analysis of numerical outcomes will be done with a multivariate linear regression model, whereas analysis of binary outcomes will be done with a multivariate logistic regression. Overall, as well as cause-specific, survival from the day of randomization, with 95% CIs, will be estimated with the Kaplan-Meier estimator. Comparison of survival between study groups will be done with a Cox regression model and hazard ratios (HR) reported with 95% CIs. Several sub-analysis with stratification by gender, age-group and other relevant categories as appropriate will be performed. Alpha level of 0.05 will be used in all analysis.

Power calculations

Currently, Registers Iceland lists 142,365 Icelanders born in the year 1975 or earlier. Assuming that 80% of them will participate in the study and that 4.2% of them will have either MGUS or LC-MGUS[13], in total 4,783 MGUS patients are expected to be found and included in the study. Power analysis for the study is based on the primary outcome of comparing survival among MGUS patients with follow-up as compared to those with no follow-up.[98] We assume that: one-third of the MGUS patients receives no follow up (per study design), two-thirds assume some follow-up, the annual baseline mortality rate for patients with no follow up is 5.6% (based on population life tables in Iceland) and the HR for the comparison with patients with follow-up is 0.81.[67] With that assumptions, and using alpha=0.05, 77.2% power is gained for rejecting the null hypothesis that the HR=1 for MGUS patients with no follow-up as compared to MGUS patients with follow up when recruiting patients for 5 years and 89.3% power is gained when recruiting patients for 7 years.

B: Progression

This part is designed to integrate current prognostic factors and correlate new molecular findings with the clinical characteristics of MGUS, genetic markers and imaging, which has the potential to provide patients with improved prognostic information, less intense follow-up for patients with low-risk disease, and improved, follow-up/treatment options for patients with high-risk disease. We plan to utilize these and other technologies in order to elucidate the natural history of MGUS and to correlate molecular findings to clinical findings in patients.

Individuals diagnosed with MGUS in arms 1 and 3 of the RCT, will constitute a study population for progression. Patients will be followed for progression and risk predictors identified. A complete history and physical examination with documentation of measurable disease (if any) and assessment of performance status using the ECOG scale will be performed. In addition Beta-2-microglobulin and CRP will be measured. During the first visit, a bone marrow biopsy and aspirate will be performed in all MGUS in arm 3 and all

except low-risk in arm 1. Bone marrow analyses will also be performed during follow-up at suspected progression. Bone marrow biopsies and one fraction of marrow aspirates will be fixed and paraffin-embedded for histological and immunohistochemical analysis and long-term storage. One fraction of marrow aspirates will be stored as air-dried aspirate smears. CD138 positive plasma cells will be isolated from a subset of these samples, and aliquots will be frozen from the aspirate supernatant, the CD138+ cell fraction, and the CD138- cell fractions for subsequent DNA, RNA, and protein analyses. Flow cytometry of bone marrow, using CD138, CD19, CD45, CD38, and CD56 and kappa/lambda will be performed. Interphase FISH cytogenetics will be done using del17p, t(4;14), t(14;16, t(11;14), and del13. Samples for gene expression profiling (GEP) and array CGH of CD138 positive plasma cells will be collected, batched, and entered into a biobank.

At each visit, following enrolment and at regular intervals, per protocol or as clinically indicated, the following will be registered or analysed: history and physical examination, performance status. Laboratory studies including: a complete blood count with differential, electrolytes, CRP, SPEP and immunofixation, FLC, and research samples.

In addition to the MGUS individuals, a control population within the non-MGUS participants, a random matched cohort, will be called in for blood analyses for comparison.

Biomarker Studies: Peripheral blood and/or urine samples from patients will be analyzed for potential serum or urine biomarkers for disease progression and correlated to clinical outcomes. Such biomarkers may include but are not limited to: monoclonal protein, free immunoglobulin light-chains, circulating proteosomes, and total immunoglobulin levels.

Information on radiological changes and progression due to bone disease will be obtained from baseline radiological examinations and follow-up examinations.

Germline risk loci

The whole genomes of 8,453 Icelanders have been sequenced using Illumina technology to a mean depth of at least 10X (median 32 X). SNPs and indels were identified and genotypes called using joint calling with the Genome Analysis Toolkit HaplotypeCaller (GATK version 3.3.0).[99] Genotype calls were improved by using information about haplotype sharing, taking advantage of the fact that all the sequenced individuals had also been genotyped with Illumina SNP arrays and long range phased. The sequence variants identified in the 8,453 sequenced Icelanders were then imputed into 150,656 Icelanders who had been genotyped with various Illumina SNP arrays and their genotypes phased using long-range phasing.[100,101] We have already MGUS diagnosis for 964 Icelanders that are part of the dataset, and will gather additional MGUS cases from the current screening study as part of this application. Individuals with MGUS will be offered to take part in the genetic part of the study, that requires an additional informed consent. Those individuals will all be Illumina array genotyped and imputed with sequence variants identified through the whole-genome sequencing of Icelanders. Logistic regression is used to test for association between the 31.6 million variants and MGUS, treating MGUS as the response and expected genotype counts from imputation or allele counts from direct genotyping as covariates in Iceland, as described previously.[102] Known risk loci for MM[27,28] and three newly described loci at 5q15 (ELL2), 5q31 (ARHGAP26), and 22q13 (HMGXB4-TOM1),[30] will be validated and new variants for MGUS identified, as described above.

Millions of hypothesis tests are performed in each genome-wide association study (GWAS), which makes them computationally demanding. Progression from MGUS to MM or other lymphoproliferative disorders is preferably estimated with sophisticated survival models, adjusted for known risk factors and even compensating for competing risks of death by other causes. The required computing power for such complicated models makes them unfeasible for GWAS studies. An innovative option is to fit a survival model a-priory to the GWAS association and feed the deviance residuals from the model as a quantitative trait in a GWAS association analysis. If the residuals are associated with a genomic variant, it can be inferred that the variant is associated with the rate of progression. This novel approach can not only be used to determine hereditary risk factors for progression from MGUS to other diseases. It can also serve as a methodological role model for identifying genetic risk factors associated with prognosis or survival for various other conditions.

Documentation and data management

The data management system used to register information from each individual from the RCT, including data from medical history, examination, and laboratory work will be designed using REDCap. REDCap (Research Electronic Data Capture) is a secure, web-based application for building and managing online research surveys and databases. REDCap is a free resource available to researchers at the University of

Iceland and their external team members. One of the investigators (ÞJL) has led the implementation of REDCap at the University of Iceland and Landspitali University Hospital.

Data storage
Data from the TBS, which includes only non-traceable codes, will be sent through a secure data sharing site. Only researcher in the study will have access to the data and data will never be transferred to another institution. All other data will be kept on servers operated by the University of Iceland in a secure data environment.

Identifier encryption
The study database will be linked to other databases using a one-way encrypted national identification number. National identifiers will be encrypted using a one-way algorithm, but with a secret code added to reduce the risk of a successful list-based brute force attack. The secret code will be destroyed after the end of the study when the data have been stored in a research data repository (safn heilbrigðisupplýsinga). Once the secret code has been destroyed there will be no method of linking the study database to individuals again.

Working plan

Estimated rate of inclusion in the screening part of the study is 300 individuals per day during the first 6 months (approximately 40 000 inclusions during first 6 months), then 150/day during next 6 months and then more slowly.

Milestones 2016

August	Study population selected from Register Iceland
	DCM selected and informed about the study design, its role and responsibilities
	Programming of study database and informed consent page done
September	Pilot project in Akranes (a town with 3,000 individuals 40 years and older

Milestones 2017

January	Letter of invitation including consent form, sent to target population
February	Info on patients agreeing to participate delivered and linked to biochemical lab database on a regular basis (once/week)
	Blood samples gathered from participating individuals throughout 2017-2019
	First patient randomized
August	Samples sent to Binding site for SPEP and FLC analyses on regular intervals through 2017-2019
	Estimated rate of inclusion is 300 per day during the first 6 months (approximately 40 000 inclusions during first 6 months), then 150/day during next 6 months and then more slowly
September	
	Continued inclusion in RCT for 3 years (during 2017-2019)
	Inclusion to the RCT estimated at a rate of 15/week

Milestones 2018

Continuous blood sampling and shipment to Binding site for analyses
Cross linkage with cancer registry and Patient registry 2 times a year
Cross linkage with information on vital status every 3 months

February	First interim analyses
March	Meeting of DCM
August	Second interim analyses
September	Meeting/TC of DCM

Milestones 2019

Continuous blood sampling and shipment to Binding site for analyses
Cross linkage with cancer registry and Patient registry 2 times a year
Cross linkage with information on vital status every 3 months
Active contact with included participants that have not donated blood samples during the first two years - continues throughout mid 2019

January	Analyses of germline variants performed (Decode genetics)

February	Third (hereafter annual) interim analyses
March	Meeting/TC of DCM
September	Imaging studies analyses

Milestones 2020

Cross linkage with cancer registry and Patient registry 2 times a year
Cross linkage with information on vital status every 3 months

February	Annual interim analyses
March	Meeting/TC of DCM
July	**Inclusion to RCT closed**
August	Bone marrow analyses performed
October	QoL analyses performed

Milestones 2021

Cross linkage with cancer registry and Patient registry 2 times a year
Cross linkage with information on vital status every 3 months

February	Annual interim analyses
March	Meeting/TC of DCM
May	Cost-effectiveness analyses
September	Analyses of impact of screening on overall survival

In summary, in this ambitious program we propose to screen for a precursor condition for the first time in a whole nation with the gain of obtaining the evidence for routine screening for MGUS and to provide real evidence for the optimal follow-up. There is considerable variation in the risk of progression, and differentiating low-risk patients, who may not need further follow-up, from high-risk patients, who may warrant close monitoring or enrolment in early intervention studies, is a challenge. The current model for progression includes only three simple factors, obtained from two simple blood tests that are all part of the definition of the disease. Molecular risk factors such as cytogenetics, germline variants, and GEP have not been included in these models nor clinical factors such as comorbidity and family history, all of which have been shown to be important in the pathogenesis of MGUS. We plan to validate current risk models for progression (for the first time in a prospective study) and aim to improve them with several novel factors, such as clinical, molecular, and genetic factors. Importantly, low-dose CT could be the optimal radiological examination for MGUS individuals, and this needs to be addressed in a prospective study. Our program will thus provide evidence to guide clinicians and patients for the optimal follow-up, and provide better prognostic scores. There is a great unmet need to answer these important clinical and scientific questions, and we foresee that this will lead to a theoretical change in the management of these disorders.

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Early achievements track-record

The PI for this application defended his thesis on familiality and prognosis in patients with monoclonal gammopathies in 2009. His PhD thesis was rewarded as the best thesis in hematology in Sweden in 2009. The PI has been working in close collaboration with researchers at Karolinska University Hospital, Karolinska Institutet, the National Institutes of Health, as well as major hematology departments in Sweden. He is in the steering board of the Nordic Myeloma Study Group (which conducts RCT in MM in the Nordic countries), a faculty member of the biannual IWWM, Organizer for the NMSG meeting in 2012, an active member of the International Myeloma Working Group, the American Society of Hematology and has held an Educational Session on MM at the American Society of Hematology´s (attendees approximately 15-18,000) annual meeting in 2010, as well as being an Abstract reviewer and a Moderator at ASH 2011 and 2013 and EHA 2013. He is also the scientific chair for the Swedish national MM registry which includes all newly diagnosed MM patients with detailed clinical, laboratory and treatment data and has published results from the registry recently in the New England Journal of Medicine. He is an author of more than 80 papers, mostly in high impact journals. He has led several very large population-based studies in Sweden, US, and Iceland. He is one of the coauthors of the updated diagnostic criteria for myeloma published by the International myeloma working group in November 2014 in Lancet Oncology, which already has 339 citations.

The PI moved to Iceland in 2012 and received a Marie-Curie carrier integration grant, and is currently the youngest professor at the Faculty of Medicine at the University of Iceland and at the Hematology Department at Landspitali University Hospital. The PIs current group includes (besides all collaborators) 6 PhD-students, 4 medical students, and a biostatistician which will continue the work on plasma cell diseases based on his past focus.

Due to his previous experience in the unique use of scientific data, high-quality research, his broad network in Europe and USA his results during the last few years have gained international attention. He will continue to perform focused studies that are based on previous findings but now involve new methods and collaborators.

Sigurdur is leading the largest meta-analyses performed in MM, including more than 4,000 patients from 14 randomized clinical trials, using individual-based data to analyse risk factors for thrombosis in myeloma as well as its effect on response and survival.

Publications

A total of 93 publications in peer reviewed medical journals, more than 100 abstracts at medical conferences. A number of publications in journals with >10 in impact factor, for example 18 in Blood (IF 10.4), 10 in JCO (IF 18.4), two in Leukemia (IF 10.4), one in Gastroenterology (IF 16.7), one in Nature Comm (IF 11.5), one in Lancet Oncology 24.7,), one in JAMA (IF35.3), one in JNCI (IF 12.5), and one Letter in NEJM (IF 55.8). A total of 2887 citations, and a h-index of 31. More than 20 publications without supervisor.

5 selected publications (1-3 without supervisor)

1. **Kristinsson SY**, Holmberg E, Blimark C. Treatment for high-risk smoldering myeloma. *The New England journal of medicine* 2013; 369(18): 1762-3. [Citations 26].

The first population-based study on smoldering myeloma. We showed that 14% of all myeloma are asymptmatic at diagnosis and that after 2 years, 57% of high-risk patients had progressed to symptomatic disease, requiring therapy. Our study supports the recent notion that these patients should be offered an early treatment strategy.

2. **Kristinsson SY**, Anderson WF, Landgren O. Improved long-term survival in multiple myeloma up to the age of 80 years. *Leukemia* 2014. [Citations 29].

This study, based on more than 40,000 myeloma patients, showed for the first time in a population-based study that survival in myeloma patients has improved in the elderly patients. These findings are of importance as they support that the novel agents have contributed to survival benefit.

3. Oddsson A*, **Kristinsson SY***, Helgason H, Gudbjartsson DF, Masson G, Sigurdsson A, Jonasdottir A, Jonasdottir A, Steingrimsdottir H, Vidarsson B, Reykdal S, Eyjolfsson GI, Olafsson I, Onundarson PT, Runarsson G, Sigurdardottir O, Kong A, Rafnar T, Sulem P, Thorsteinsdottir U, Stefansson K. The germline sequence variant rs2736100_C in TERT associates with myeloproliferative neoplasms. *Leukemia* 2014. ***contributed equally.** [Citations 24].

In this study, we performed whole genome sequencing of 2,230 Icelanders followed by imputation of 34.2 million sequence variants into a set of Icelandic Philadelphia chromosome negative MPN cases (N = 237) and controls (N = 34 128). The germline variant rs2736100_C (allele frequency = 49.3%) in the second intron of the TERT gene, encoding telomerase reverse transcriptase, were associated with MPN

(odds ratio (OR) = 2.09, P-value = 6.4 x 10-10). The variant has a similar effect on the three MPN sub-phenotypes polycythemia vera (OR = 2.32), essential thrombocythemia (OR = 2.21) and primary myelofibrosis (OR = 2.42). In individuals without MPN the variant also associates with high count of red blood cells, platelets and white blood cells of the myeloid but not of the lymphoid linage. We did not detect a correlation between JAK2V617F somatic mutation status and rs2736100_C. Our findings provide novel insight into the pathogenesis of MPNs.

4. Lindqvist EK, Goldin LR, Landgren O, Blimark C, Mellqvist UH, Turesson I, Wahlin A, Bjorkholm M, **Kristinsson SY**. Personal and family history of immune-related conditions increase the risk of plasma cell disorders: a population-based study. *Blood* 2011; 118(24): 6284-91. [Citations 31].

In this paper we showed that a personal history of autoimmune disease is a risk factor for MGUS and some specific disease are associated with myeloma. In addition we saw that for the first tume that a family history of autoimmune disease increases the risk . Our findings suggest that immune-related conditions and/or their treatment are of importance in the etiology of MGUS and possibly MM. The association of both personal and family history of autoimmune disease with MGUS indicates the potential for shared susceptibility for these conditions.

5. **Kristinsson SY**, Pfeiffer RM, Bjorkholm M, Goldin LR, Schulman S, Blimark C, Mellqvist UH, Wahlin A, Turesson I, Landgren O. Arterial and venous thrombosis in monoclonal gammopathy of undetermined significance and multiple myeloma: a population-based study. *Blood* 2010; 115(24): 4991-8. [Citations 99].

Using population-based data from Sweden, we assessed the risks of venous and arterial thrombosis in 18,627 MM and 5,326 MGUS patients diagnosed from 1958 to 2006, compared with 70,991 and 20,161 matched controls, respectively. At 1, 5, and 10 years after MM diagnosis, there was an increased risk of venous thrombosis and arterial thrombosis. Patients with MGUS also had an increased risk (although lower) of venous an darterial thrombosis. IgG/IgA (but not IgM) MGUS patients had increased risks for venous and arterial thrombosis. Our findings are of relevance for future studies and for improvement of thrombosis prophylaxis strategies.

Presentations

Several presentations at hematological conferences, including 1-4 abstracts at annual ASH and EHA meetings, both as oral and poster presentations. Invited speaker to ASH 2010, and to Universities in Denmark, Sweden, Spain, Norway and USA.

Prizes and memberships

Several prizes for medical research including best academic thesis in hematology in Sweden 2009, Annual Encouragement Grant at Landspitali University Hospital in 2013, Prize as an outstanding medical researcher at University of Iceland and Landspitali 2014. Award for research on lymphoproliferative diseases from the Swedish Society of Hematology in 2009. Award for teaching medical students at the Karolinska University Hospital 2003. Award for best scientific contribution by a medical student at the Icelandic Medical Congress in 1998.

Member of the European Hematology Association, the American Society of Hematology, Swedish hematology Association, International Myeloma Working Group, the Black Swan Initiative, the International Waldenström Working Group. In the editorial Board for the Hematopics (EHA newsletter).

To summarize, the PI has during his 6 years since dissertation, published several papers in high-impact peer-reviewed journals, led several international projects in the field, and has frequently been invited as an invited speaker at large hematology conferences. He has established his supervisor skills and scientific creativity by using novel approaches to answering important scientific gaps in the literature. His prior research has shed light on several risk factors, complications and outcomes of patients with MM and its precursor. This proposal of screening and performing a RCT in MGUS is yet another example of the PI´s forward thinking in respect of medical and scientific advances.

Curriculum Vitae

PERSONAL INFORMATION

Family name, First name: Kristinsson, Sigurdur

Researcher unique identifier: M-2910-2015

Date of birth: May 16 1973

Nationality: Icelandic

Current position: Professor in Hematology at the University of Iceland and Senior registrar at department of Hematology, Karolinska University Hospital, Sweden

Education

PhD in hematology June 2009: "Population-based studies on familiality and prognosis in patients with hematological malignancies": Karolinska Institutet, Sweden. Supervisor: Prof. Magnus Björkholm.
Specialist in hematology – Karolinska University Hospital, July 2007
Specialist in internal medicine - Karolinska University Hospital, September 2006
Graduated from medical school from the University of Iceland in 2000
Graduated from College in Reykjavík in 1993
Postdoc at Karolinska Institute/Karolinska University Hospital from 2009-2012

Awards

Award from the research fund of Þórður Harðarson and Árni Kristjánsson as an outstanding researcher 2015
Awards for best academic thesis in hematology in Sweden 2009
Award for teaching medical students at the Karolinska University Hospital 2003
Award for best scientific contribution from a medical student at the Icelandic Medical Congress in 1998

Grants

Number of grants for research on lymphoproliferative diseases, mainly plasma cell diseases, for example from Marie-Curie reintegration grant (EU), the Swedish Cancer Society, the Karolinska Institutet Foundations, Swedish Hematology Association, and the Icelandic Centre for Research (RANNIS).

Working

Current position: Professor in Hematology at the University of Iceland and Senior registrar at department of Hematology, Landspitali University Hospital, from September 2012.
Senior registrar, Hematology Centre, Karolinska University Hospital, Stockholm, Sweden, from October 2010 to August 2012 (50% research).
Clinical hematologist, Hematology Centre, Karolinska University Hospital, Stockholm, Sweden, from July 2007
Fellowship in hematology at Hematology Centre, Karolinska University Hospital, Stockholm, Sweden from September 2002

Teaching

PhD-Supervision at Karolinska University Hospital:
Malin Hultcrantz: Epidemiological and clinical studies on patients with myeloproliferative neoplasms (Dissertation 2013).
Cecilie Blimark: Clinical and population-based studies in multiple myeloma and monoclonal gammopathy-with focus on infections (Dissertation 2014).

Current PhD-students
Christian Kjellander (registered 2013 at Karolinska): Infections in patients with hematological malignancies.
Ebba Lindqvist (registered 2013 at Karolinska): Monoclonal gammopathies: Risk factors and complications.
Gudbjörg Jonsdottir (registered 2014 at University of Iceland): Secondary malignancies in myeloma patients.
Caroline Weibull (registered 2014 at Karolinska): Comorbidity in patients with haematological malignancies
Marianna Thordardottir: Risk factors for MGUS (registered 2014 at University of Iceland)

Vilhjalmur Steingrimsson (registered 2015 at University of Iceland): Chronic lymphocytic leukemia-survival and comorbidity.
Sigrun Þorsteinsdottir (registered 2015 at University of Iceland): Bone disease and outcome in patients with MGUS and myeloma

Supervisor for several medical students and pharmacology student for project research.
Courses on epidemiology and statistics, 20 weeks (30 University credits) at Karolinska 2006-2008.
Clinical teaching:
Clinical teaching assistant for medical students in Clinical Medicine at Karolinska Institutet from January 2009-2011 (50% of fulltime=adjunct).
More than 300 lectures at Karolinska Institute for medical students.
Responsible for fellowship education at Hematology Centre 2005-2006.
Journal club: Responsible for weekly journal clubs at Hematology Unit 2009-2010.
Course on the Science of Education for University Teachers with focus on Medical students and clinical working (5 weeks), 7,5 University credits.

Examinations:
Supervisor for constructing and evaluating written examination on Swedish national examination in internal medicine for interns in 2009 and 2011 (n>200)
Supervisor for constructing and evaluating written and bedside examination on TULE examination for non-EU (n>150) MDs applying for Swedish board examination 2009-2014.
Responsible for Final Examinations in Internal Medicine for Medical students in Stockholm 2009-2011.

Lectures

Invited speaker for several national and international meetings.
Education session in American Society of Hematology, annual meeting, Orlando 2010.
International workshop on Waldenström macroglobulinema, Stockholm 2008, Venice 2010, and USA 2012, and United Kingdom 2014.
Multiple Myeloma and Related Malignancies, Educational Course, Bari, Italy 2011.
Nordic Myeloma Study Group meeting, Iceland 2012
Danish Lymphoma Group meeting 2012.
Several meetings on multiple myeloma and related disease in Sweden 2009-2014.
Over 200 hours of lectures on hematology, mainly benign, acute hematology and plasma cell disorder for medical students.

Administration

Faculty member of the biannual International Working group on Waldenström Macroglobulinemia
Member of the International Multiple Myeloma Working Group (IMWG),
Member of the American Society of Hematology
Member of the European Hematology Association
Responsible for the Swedish national MM registry
Reviewer for abstract for ASH annual meeting in 2011 and 2013, clinical myeloma session
Reviewer for abstract for EHA annual meeting in 2012 and 2014, clinical myeloma session
Reviewer for abstract for Nordic Myeloma Study Group meeting, Iceland 2012
Member of the admission board for PhD students at the Karolinska Institutet from 2007
Clinical teaching assistant for medical students in Clinical Medicine at Karolinska Institutet from January 2009 (50%) to August 2010.
Principal organizer for a Hematology Meeting on c-myc and p53 at Karolinska Institutet October 2010.
Moderator for Oral Session at ASH 2011, San Diego, USA
Regular reviewer for several peer-reviewed journals including JAMA, Blood, Haematologica, Blood review, Leukemia, Medical Oncology, American Journal of Hematology, Acta Haematologica, Leukemia and Lymphoma, and the Swedish Medical Journal.

Publications

More than 90 articles.
Google Scholar: https://scholar.google.is/citations?user=4nfGC94AAAAJ&hl=en&oi=ao
H-index: 36