Diagnosis and classification of axial spondyloarthritis : imaging and non-imaging features

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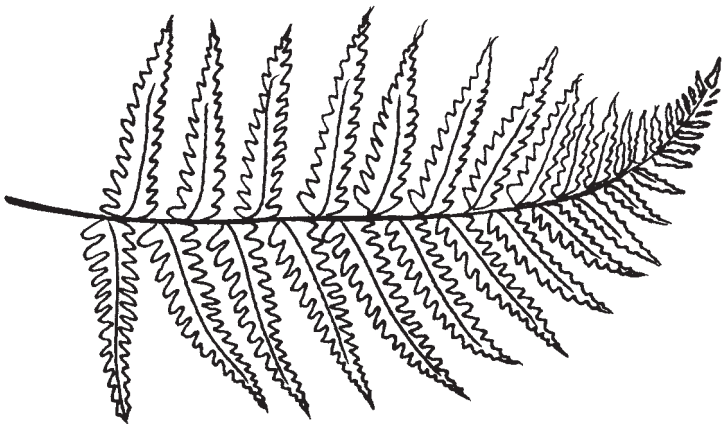
Summary and general discussion



SUMMARY AND GENERAL DISCUSSION

All studies described in this thesis cover various aspects of the diagnostic work-up of patients with chronic back pain suspected of having axial spondyloarthritis (axSpA) and the diagnosis and classification (according to the ASAS classification criteria) of axSpA. Moreover, these studies are centralized around the same objective, being the early recognition and diagnosis of axSpA.

The following topics were addressed. First, the diagnostic process in chronic back pain patients and the final diagnosis of axSpA were elaborately evaluated in a secondary/tertiary care setting. Second, the use and potential added value of spinal MRI for the classification of axSpA (according to the ASAS criteria) was tested. Finally, we focus on the diagnostic process again and evaluated the role of imaging findings as a whole in the diagnosis and classification of (early) axSpA: We investigated the use of sacroiliac imaging in clinical practice for diagnosing axSpA, but also the influence of different readings by local assessors and central readers on the classification of axSpA.

All studies presented in this thesis were performed in two cohorts: the DEvenir des Spondyloarthropathies Indifférenciées Récentes (DESIR)[1] and the SpondyloArthritis Caught Early (SPACE)[2] cohorts. These cohorts were collected with more or less similar study protocols as all patients underwent a full (fixed) diagnostic work-up at pre-defined time points to assess disease characteristics and the presence of all SpA features. However, there are also important differences between the two cohorts. The SPACE cohort is a multicentre, multinational (the Netherlands, Norway, Sweden, Italy) observational study, whilst the DESIR cohort is a national French observational cohort with multiple (25) participating centres across the country. Furthermore, the SPACE cohort includes patients with a minimum age of 16 years who had chronic back pain of short duration (between three months and two years), and with an age of onset before 45 years. DESIR, however, included patients between the ages of 18 and 50 years with chronic *inflammatory* back pain (IBP, duration between three months and three years) and a substantial suspicion of axSpA (measured by a physician's level of confidence in a diagnosis of at least five on a zero to ten scale). In SPACE all patients with chronic back pain (and not only those with IBP) can be included, regardless of an existing suspicion of axSpA. In addition, inclusion of patients in DESIR is now closed (inclusion took place between December 2007 and April 2010), whilst SPACE is an ongoing cohort study still actively recruiting patients. For this thesis, however, only baseline and one-year follow-up data from the SPACE cohort and only baseline data from the DESIR cohort were used.

In this final chapter we summarize the main findings of the studies presented in this thesis. Thereafter, we will discuss future perspectives and devise research questions that may further our knowledge of axSpA.

Diagnosis of axSpA

The timely recognition of axSpA – especially in an early disease stage – is challenging as the disease is heterogeneous in its presentation and confirmatory signs or symptoms, in analogy to for instance urate crystals in the joint in patients with gout, are lacking. An important phase in the diagnostic process of patients with continuous chronic back pain is the collection of information regarding a patient's present status and rheumatologic history. Patients should be inquired about past or present conditions that are relevant to axSpA (i.e. SpA features). Inflammatory back pain (IBP) is a common feature and has several definitions.[3-5] However, in this thesis IBP is deemed 'positive' or present when at least four of the following characteristics are present: an onset before the age of 40 years, an insidious onset, improvement with exercise, no improvement with rest, and pain at night, i.e. fulfilment of the ASAS criteria for IBP.[6] Furthermore, patients may complain about heel pain suggestive of enthesitis, peripheral arthritis, or swollen and painful toes or fingers suggestive of dactylitis.[7-10] The concurrent presence or history of extra-articular manifestations, being acute anterior uveitis, inflammatory bowel disease (IBD), and psoriasis also increases the likelihood of axSpA.[11, 12] In addition, a positive family history of SpA (i.e. the presence of AS, psoriasis, acute anterior uveitis, reactive arthritis, or IBD in first- or second-degree relatives) and a good response (i.e. relief of pain symptoms) to non-steroidal anti-inflammatory drugs (NSAIDs) are considered useful characteristics in the diagnostic assessment of CBP patients. [13] Next to interviewing the patient, a thorough physical examination is required to objectively assess the presence of the aforementioned clinical features. Importantly, there is no single laboratory test to diagnose axSpA. However, the presence of human leukocyte antigen-B27 (HLA-B27) and/or an elevated acute phase reactant (C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)) that cannot be explained by another condition, may further point to a diagnosis of axSpA. Finally, characteristic findings on radiographs or MRI of the sacroiliac (SI) joints may frequently be seen.

Neither a formal diagnostic standard for axSpA nor diagnostic criteria exist, so all signs and symptoms of axSpA presented by patients – either present or absent – should be appreciated and weighted in an aggregated manner (full clinical context) by the diagnostician in a rather intuitive process of pattern recognition.[14, 15] This implies that the assessing rheumatologist has broad expertise in diagnosing axSpA and its differential diagnoses, that he knows about

types and has access to relevant laboratory tests and imaging. A previously discussed tool, the modified Berlin algorithm, is an example of how a decision tool can support clinicians in such a process, but should not be followed blindly.

If the algorithm would be used strictly as a means to diagnose axSpA, it would result in approximately 10 percent false-positive cases but 10 percent of cases will be missed (false-negative cases) when compared against the rheumatologist's (i.e. expert's) diagnosis.[16]

The ASAS classification criteria for axSpA are frequently used to define patients for inclusion in studies. As the classification criteria were developed in a controlled setting with an artificially high prevalence of axSpA, experts have repeatedly warned against the use of these *classification* criteria for *diagnosing* axSpA.[17] Still, as diagnosing axSpA early remains a continuous challenge, concerns about inappropriate use of the ASAS classification criteria in clinical practice remain. The classification criteria have been developed with the diagnosis of a clinical 'expert panel' as the external standard in the absence of a real gold standard. Expert opinion includes patient characteristics and symptoms at presentation that are combined with results from selected laboratory tests and imaging findings. The underlying process is that of 'pattern recognition' in which physicians (i.e. rheumatologists) conscientiously (or unconscientiously) use their clinical experience to try and put all the 'pieces of the (axSpA) puzzle' together. The application of the classification criteria to diagnose axSpA in clinical practice scenarios with low pre-test probability may lead to significant *overcall*. And especially in low prevalence settings and in circumstances with little experience with axSpA, such as primary care settings, it is tempting to use classification criteria to make a diagnosis. As a complicating factor, there is a thin line between classification and diagnosis since most clinical, laboratory and imaging results are used in both classification and diagnosis of axSpA. Nevertheless, the classification criteria should be used in patients *already* diagnosed with axSpA. And part of this diagnostic process also includes the exclusion of other, more likely diagnoses.

As said, the sheer counting of SpA features – i.e. *ticking boxes of features and symptoms* – whilst neglecting more likely alternative diagnoses (differential diagnosis) may easily lead to *overdiagnosis* of axSpA, which may in turn invoke inappropriate medical treatment.[17-19] Concerns raised by experts of misdiagnosis and in particular *overdiagnosis* have led to the research in **Chapter 2**. In this chapter – bearing the aforementioned concerns in mind – we investigated whether the presence of multiple SpA features in a chronic back pain patient has always led to axSpA diagnosis. We have studied which SpA features contributed most to an axSpA diagnosis and we assessed the agreement between the rheumatologist's diagnosis

and the ASAS classification criteria in the SPACE cohort. In this study 500 patients, after undergoing a full diagnostic protocol, were stratified according to the number of SpA features: 159 (32%) had less than or equal to one feature, 143 (29%) had two features, 79 (16%) had three features and 119 (24%) had four or more features. Half of the total study population was diagnosed with axSpA, and the likelihood of an axSpA diagnosis was generally conditional upon the number of SpA features. Still, numerous patients with multiple SpA features were not diagnosed with axSpA. These findings show that making a clinical diagnosis of axSpA is more than a simple summation of SpA features. Overdiagnosis merely based on the presence of multiple SpA features is a concern but likely did not occur frequently in centres participating in the SPACE cohort in which experts judged the diagnosis.

There were also encouraging findings showing that rheumatologists are not blindly guided by classification criteria. HLA-B27 negative patients without imaging abnormalities (either radiography or MRI of sacroiliac joints) and few other SpA features could still receive a diagnosis of axSpA without classifying as axSpA. A potential explanation for these diagnoses is that other features or symptoms (not part of the ASAS classification criteria), such as alternating buttock pain or the presence of spinal inflammatory lesions, were rated as relevant features for a diagnosis of axSpA. In addition, rheumatologists may have based their diagnosis on their own interpretation of the imaging in combination with the clinical picture. Another interesting question raised in this study was *which* SpA features were most contributory to axSpA diagnosis. In both univariable and multivariable analyses we found that 'HLA-B27 positivity' and 'any positive imaging' (i.e. either sacroiliitis on a radiograph or MRI) were independent determinants of an axSpA diagnosis. Especially positive imaging of the sacroiliac joints was a dominant feature. These results underline the importance of proper interpretation of imaging or new imaging modalities (discussed later) in the diagnostic process of axSpA. With the concern of just '*ticking boxes*' for axSpA diagnosis in mind, we have also looked at the relation between axSpA diagnosis and classification according to the ASAS axSpA criteria. For this, the diagnosis of the treating rheumatologist was used as a gold standard to test the performance of the ASAS axSpA classification criteria. The ASAS classification criteria had an overall sensitivity and specificity of 76% and 84%, respectively. These results were a bit worse than those published in a recent systematic literature review and meta-analysis in which the performance of the ASAS axSpA criteria was summarized.[20] A sensitivity of 82% and a specificity of 88% were reported, which is indeed in line with the aforementioned conclusion that not all patients with a diagnosis of axSpA are classified as such, and vice versa.

The differentiation of the signs and symptoms of axSpA from other conditions which may also present with CBP is important in the diagnosis of axSpA. In addition, some conditions may well co-exist with axSpA. The differential diagnosis for axSpA includes among others mechanical back pain, osteitis condensans ilii, sacroiliac joint infection, diffuse idiopathic skeletal hyperostosis (DISH), degenerative disc disease, and fibromyalgia.[21-24] During follow-up, the clinical presentation of CBP patients might change, which can result in the rheumatologist either refuting the initial diagnosis –axSpA or an alternative diagnosis – or getting increased confidence in the initial diagnosis. In **Chapter 3** we further elaborate on the findings in **Chapter 2,** mainly on the clinical characteristics and alternative diagnoses of patients who were not diagnosed with axSpA, especially in those with four or more SpA features who are considered as having axSpA by the Berlin algorithm. This study was prompted by the comments of Braun *et al.* in Nature Reviews in which they state that it is unlikely that a patient with four or more SpA features does not have SpA.[25] In the SPACE cohort rheumatologists are asked to provide a clinical diagnosis (axSpA or no axSpA). In case of 'no axSpA' rheumatologists were requested to provide a better alternative diagnosis. In all patient categories (those with no- or only with one- SpA features versus those with two, three, and four or more SpA features) the most frequent alternative diagnoses were expectedly non-specific back pain, mechanical back pain, degenerative disc disease, and (fibro)myalgia. None of the 18 patients with four or more SpA features had imaging abnormalities suggestive of axSpA and only four of them were HLA-B27-positive. Furthermore, they had SpA features that are considered less specific, such as IBP, a positive family history for SpA, and a good response to NSAIDs. These findings reassuringly suggest that – although an axSpA diagnosis is likely in the presence of a high number of SpA features – rheumatologists may still discard the diagnosis when they think there are not enough arguments in favour of a diagnosis.

As mentioned before, the definite diagnosis of axSpA is preceded by an elaborate work-up of imaging, physical examination, and laboratory testing. However, despite this extensive diagnostic approach, uncertainty regarding the diagnosis (diagnostic uncertainty) is not uncommon. In **Chapter 4** we looked into diagnostic uncertainty at baseline and after one-year follow-up, and at the possible influence of SpA feature accrual on diagnosis. An important finding of this study was that diagnostic uncertainty was common, however standardized (one-year) follow-up led to a decrease of patients with uncertain diagnosis. Importantly, some uncertainty regarding the diagnosis remained at follow-up. Almost half of the patients had developed at least one SpA feature after one year, but this did in most cases not lead to changes in diagnosis or level of certainty. These results may reflect certain aspects of clinical reasoning in daily rheumatologic practice. First, the finding that the acquisition of new SpA

features after one year did not necessarily lead to a switch of diagnosis can be the result of rheumatologists 'weighing' SpA features in importance. Positive imaging suggestive of axSpA might be considered a 'stronger' SpA feature than 'good response to NSAIDs'. Second, rheumatologists may base their diagnosis and level of certainty on other features than the SpA features defined in the ASAS axSpA criteria. The definition 'diagnostic uncertainty' was construed by an arbitrarily chosen cut-off value as there is no clear definition nor a way to scientifically measure diagnostic uncertainty. An interesting conclusion we may draw from our data is that at baseline rheumatologists hypothesize about the possible diagnosis which can be influenced by newly acquired information of or from the patient. Diagnostic uncertainty is not necessarily a 'bad thing' albeit that excessive use of health care resources in the pursuit of a diagnosis should be avoided. Therefore, in cases with diagnostic uncertainty a "wait and see approach" is justified.

One of the commonly present SpA features is a positive family history. The definition of a positive family history, as is used in daily clinical practice as well as in research studies, has once been constructed by a panel of SpA experts, but was never validated. **Chapter 5** discusses the usefulness of the current definition of a positive family history (PFH) as it is considered a risk factor for axSpA, and whether the five diseases that comprise a PFH contribute equally well to diagnosing axSpA. For this study data from both the SPACE and DESIR cohorts were used. In both cohorts a PFH was defined according to the definition used in the ASAS classification criteria: the presence of ankylosing spondylitis (AS), acute anterior uveitis (AAU), reactive arthritis, inflammatory bowel disease (IBD), and psoriasis in first- or second-degree relatives (first-degree: mother, father, sister, brother, daughter, son); second-degree: aunt, uncle, niece, nephew, grandmother, and grandfather).[5] Overall, the most common diseases among first-or second-degree relatives were AS and psoriasis, followed by IBD, AAU, and reactive arthritis. In both univariable and multivariable analyses a PFH of AS or AAU was independently associated with HLA-B27 positivity. These results were expected since AS and AAU have a known association with HLA-B27.[26-28] Furthermore, AAU showed an association with axSpA diagnosis in SPACE only. In addition, there was no association of PFH with sacroiliitis on imaging. We also looked at the relative contribution of HLA-B27 among patients who were classified according to the ASAS axSpA criteria. The majority of these patients were HLA-B27 positive. Interestingly, a PFH was more often reported in HLA-B27 positive patients compared to HLA-B27 negative patients. We concluded that a PFH of AS or AAU may be useful for case-finding in low prevalence settings as they are correlated with HLA-B27 carriership. However, a PFH of reactive arthritis, IBD, and psoriasis does not contribute to diagnosing axSpA in CBP patients suspected of axSpA. A recent study by van Lunteren *et al*. replicated

this finding in the ASAS cohort. They expanded their research question to ethnicity and degree of family relationship (i.e. first or second degree relatives), and found that a PFH of AS was positively associated in all patient subgroups, but that there was no association between a PFH of AAU, ReA, IBD or psoriasis with HLA-B27 carriership.[29] These findings are well in line with ours in that a PFH of AS, and possibly of AAU, may '*track*' patients who are at risk of having axSpA. These patients should subsequently be typed for HLA-B27. Furthermore, these findings underscore calls that the current definition of a PFH for this specific population should be amended.

Use of imaging in the diagnosis of axSpA

One of the most important aspects in the (early) diagnosis (and classification) of axSpA is the use of imaging (conventional radiography and MRI of the sacroiliac joints) to assess active inflammation and/or structural changes highly suggestive of axSpA. An important limitation is that patients may have symptoms long before abnormalities (i.e. sacroiliitis) are detected on radiographs.[5, 10, 30] Another important consideration is that not all patients with axSpA will develop structural lesions in the sacroiliac joints or the spine. MRI was introduced to overcome some of these issues in an early disease phase, since MRI may visualize both structural and inflammatory lesions in the sacroiliac joints and the spine.[31-34] The introduction of MRI has spearheaded the distinction of a fairly new disease entity called 'non-radiographic axSpA'. Numerous studies have investigated this imaging modality in axSpA during the past decade.[35] ASAS has developed several recommendations on how to best perform an MRI of the sacroiliac joints and a definition for a positive MRI.[14, 33] Because of the widespread use of sacroiliac imaging, a correct interpretation of the imaging by either an experienced rheumatologist or a radiologist is of crucial importance. There are several concerns, however, regarding the use of sacroiliac imaging. The recognition of sacroiliitis on radiographs is unreliable, regardless of the experience or training of the assessor(s).[36, 37] Inaccurate readings (i.e. false-positive or false-negative for sacroiliitis) may lead to wrong diagnoses, especially if a diagnosing physician would rate the importance of abnormal imaging higher than the presence or absence of clinical symptoms. Subsequently, such falsely diagnosed patients may be enrolled in clinical trials or other types of clinical research, since they may erroneously classify as positive using the ASAS classification criteria. We do not have much insight into the extent to which rheumatologists are led by imaging findings in diagnosing their patients with axSpA.

The ASAS experts, who have developed the ASAS classification criteria for axSpA, did not include spinal inflammatory lesions on MRI (MRI-spine) as an imaging criterion in the classification of axSpA.[5] However, several studies have shown that spinal inflammatory lesions

may occur, even in the absence of sacroiliitis on MRI.[38-40] Given these observations, it was of interest to investigate whether MRI-spine should have a place as an element in the ASAS classification criteria. A consensus definition for a positive MRI-spine (i.e. three or more spinal inflammatory lesions) had already been developed by the ASAS/Outcome Measures in Rheumatology (OMERACT) MRI working group.[39] A positive MRI-spine is defined as the presence of ≥3 inflammatory lesions in the vertebrae on ≥2 consecutive slices. Recently, a new cut-off value (the 'rule of five') for spinal inflammatory lesions - positive MRI-spine defined as ≥5 inflammatory lesions - was proposed by the Hooge *et al.* that had a higher specificity (> 95%).[41] In **Chapter 6** we wanted to investigate whether it is useful to add a positive MRI-spine as an imaging criterion in the ASAS classification criteria for axSpA. Baseline data from both the SPACE and DESIR cohorts were used and several definitions of a positive MRI-spine were applied: (1) the ASAS consensus definition (≥3 spinal inflammatory lesions); (2) 'rule of five' - ≥5 spinal inflammatory lesions; (3) SPARCC-score of ≥5 by at least two readers (not available in DESIR); (4) and SPARCC-score of ≥5 by the mean of three readers (not available in DESIR). The majority of chronic back pain patients did not have any imaging abnormalities suggestive of axSpA. An isolated positive MRI-spine according to the 'rule of five' definition was found in only 1% and 2% of patients in the SPACE and DESIR cohorts, respectively. Almost all patients already had fulfilled the ASAS-criteria through the clinical arm. In both cohorts only one patient could additionally be classified as having axSpA by a putative MRI-spine-enriched imaging arm. This implies that a huge number of MRI-spine have to be performed needlessly in order to additionally classify one patient. We arrived at similar conclusions when using the other definitions for a positive MRI-spine. Therefore, the use of MRI-spine in the *classification* of axSpA is not recommended. An important side note is that this study focused on the effect of adding MRI-spine to the ASAS classification criteria. We did not formally assess the role of MRI-spine for an axSpA diagnosis in routine clinical practice. Obviously, MRI-spine may still be valuable for excluding other diseases with chronic back pain (differential diagnosis). We have also not investigated if MRI-spine is of added value in establishing the *activity* of the disease, for instance for monitoring purposes. This remains to be investigated.

In daily clinical practice the diagnosis of axSpA relies on local reading of images, usually in the clinical context, by either the radiologist and/or rheumatologist. In contrast, research studies use (blinded) centralized readers who have been trained and calibrated well. In **Chapter 7** we replicated a previously performed study in DESIR to investigate whether reading discrepancies between local assessors and central readers influenced the classification of chronic back pain patients in the SPACE cohort.[42] In our study we confirmed that local assessors and central readers did not agree on the presence of sacroiliitis on MRI in 81/513 (16%) of patients. For

sacroiliitis on radiographs this rate of disagreement was 55/513 (11%) patients. Discrepant read-results led to a different classification in 52/513 (10%) patients, which is not negligible but also not of major impact. With central reading as external standard we found that local assessors tended to overrate the presence of sacroiliitis leading to a certain false-positive rate ('local overcall'). These findings were essentially similar to those reported in DESIR and add to the conclusion that the ASAS classification criteria are reasonably robust against differences invoked by local versus central readers. That read-discrepancy did not have a greater impact is mainly due to the inclusion of the *clinical arm*, which mitigates a wrong classification based on the imaging arm only.

Chapter 8 is the last chapter addressing the use of imaging in clinical practice, particularly sacroiliac imaging, in the SPACE cohort. Moreover, the effects of imaging results on the diagnosis and diagnostic confidence of rheumatologists were studied here. According to a fixed protocol rheumatologists were asked to provide a diagnosis *before* and *after* imaging results were known, and a corresponding level of confidence regarding this diagnosis. Sacroiliac imaging was interpreted by local assessors (rheumatologists & radiologists). Before imaging results were known to rheumatologists more than half of the patients (62%) had already been diagnosed with axSpA. As we have shown before in **Chapter 3** most common diagnoses in the patients *not* diagnosed with axSpA were non-specific back pain, degenerative disc disease or mechanical back pain. Expectedly, axSpA patients were more often male, HLA-B27 positive, and had more SpA features than patients without axSpA. Both in the groups with and without the diagnosis of axSpA, the mean (SD) level of confidence (LoC) was moderate at best (axSpA LoC 6.6 (SD 1.9), no axSpA LoC 5.6 (2.0)). After studying the results of the imaging, rheumatologists refuted the previous axSpA diagnosis in a number of cases. In total, after studying the results of imaging, 109/513 (21%) patients were assigned a different diagnosis, but the level of confidence regarding their (new) diagnosis markedly increased. Our findings suggest that imaging results play an important role in the diagnostic considerations of rheumatologists and increase the confidence in a diagnosis, regardless of the imaging outcome (positive or negative). This observation is in line with the conclusion of **Chapter 2,** namely that there is a strong relation between sacroiliitis on imaging and an axSpA diagnosis. In addition, imaging results increase their level of confidence with which they conclude to a certain diagnosis.

Future perspectives for research and implications of findings

A clear challenge in Rheumatology is making an appropriate diagnosis of axSpA early in patients presenting with chronic back pain. The timely presentation of patients to the rheumatologist is dependent on primary care physicians and other workers in primary health

care (physiotherapists and others). Although not covered in this thesis, an early identification and timely referral of chronic back pain patients is pivotal. Increasing awareness of the existence of axSpA may guide patient and doctor toward a timely diagnosis. This thesis has provided elements that may be of help in this regard. An important limitation of our studies, however, is that the conclusions cannot be extrapolated to primary care and common Rheumatology practice without further consideration since they have been derived from researching the SPACE and DESIR cohorts. These are cohorts with a far higher prevalence of axSpA than any clinical setting. It would be interesting to analyse how an axSpA diagnosis is made in settings with a lower prior probability, whether the modified Berlin diagnostic algorithm has indeed a place in the diagnostic process and whether the number of present SpA features dictates the diagnosis.

We have seen that positive imaging and the presence of HLA-B27 often drive a diagnosis of axSpA by rheumatologists in clinical practice. Which SpA features were considered most important for a diagnosis by rheumatologists, however, was not assessed. It is, for instance, very likely that rheumatologists weigh different SpA features differently and this may have (had) impact on the final diagnosis. Analysing such 'heterogeneity amongst diagnosticians' may give us better insight into how a diagnosis of axSpA is made and what it means. Such a process may even lead to considering other or new features or symptoms in diagnosing axSpA.

As we try to be more efficient in our daily clinical practice we wondered whether several aspects of the current definition of a positive family history (PFH) are relevant for case-finding (or axSpA diagnosis). Of note, a PFH is usually patient-reported which may both lead to an underestimation (patients cannot remember) or to an overestimation (patients misinterpret chronic back pain in a family member as a symptom of axSpA). Further clinical research is needed here in order to better diagnose axSpA. In addition, the current definition of a PFH (in this specific population) in the classification criteria deserves reconsideration and possibly modification. Ultimately, an interesting topic for future clinical research will be to investigate if certain combinations of SpA features point to axSpA with higher likelihood than others. Altogether, this may lead to earlier and more appropriate diagnosis and treatment of axSpA in different clinical settings.

The use of conventional radiography and MRI for an axSpA diagnosis (and subsequent classification) remains a point of debate. An important remaining question is when to use which modality and whether it does make a difference for the early recognition of axSpA. There have been recent studies assessing the course and progression of imaging abnormalities as well

as the development of new lesions over time. Ideally, in a few years we may predict which patients will develop structural bone lesions or permanent damage. Such a risk-stratification may lead to an individualized treatment plan (*personalized medicine*) and follow-up for each patient. Both cohorts used in this thesis (SPACE and DESIR) have longitudinal data and may help – in time – provide us with the answers.

Final comments on this thesis

In this thesis the focus was on diagnosing axSpA early using clinical features as well as imaging modalities. We have studied multiple elements diagnosing axSpA among patients presenting with chronic back pain. We have emphasized two main themes: (1) the importance of clinical SpA features; and (2) the contribution of imaging to an axSpA diagnosis and classification. We have learned how rheumatologists use imaging results in their diagnostic considerations and thereby have helped reduce certain fears regarding the way diagnosis is made in clinical practice. We have shown that the use of MRI-spine in classification is not efficient. The common thread in all of the studies in this thesis is that axSpA diagnosis is the interaction between the clinical aspects of chronic back pain and imaging findings highly suggestive of axSpA. Clinicians should be aware of mindlessly 'stacking up' SpA features in chronic back pain patients in order to avoid unnecessary (biologic) treatment. Additional studies are needed to investigate the numerous phenotypes of axSpA and to predict in which chronic back pain patient axSpA diagnosis is likely. Overall, we hope the studies reported in this thesis will contribute to a better understanding of how we diagnose axSpA in daily clinical practice as this is likely an important step towards improving long term outcomes of patients with axSpA.

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