**A Delphi study on the Use of Technology in the Subcategorisation of Osteoarthritis**

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**Running Headline**

Subcategorising Osteoarthritis

**ABSTRACT**

**Objective**

This study utilised a Delphi consensus process within the OATech Network+ to identify whether existing technology could aid subcategorisation of patients with osteoarthritis (OA) and determine the level of awareness of these technologies across the expert panel.

**Design**

An online questionnaire was formulated based on technologies which may aid subcategorisation of OA. A two-day face-to-face meeting was held to monitor concordance of expert opinion with online surveys (23 questions) completed before (Round 1), during (Round 2) and at the end of (Round 3) the meeting. Experts spoke at the start of the meeting on imaging, genomics, epigenomics, proteomics, metabolomics, biomarkers, activity monitoring, clinical engineering and machine learning. For each round of voting, ≥80% votes led to consensus and ≤20% votes led to exclusion of a statement.

**Results**

Panel members were unanimous that technological advances can improve OA subcategorisation. . It was agreed at Rounds 1 and 2 that epigenetics, genetics, MRI, proteomics, wet biomarkers and machine learning could all aid subcategorisation. Talks from experts changed participants’ opinions on the usefulness of metabolomics, activity monitoring and clinical engineering, reaching consensus in Round 2. X-rays lost consensus between Rounds 1 and 2 but their use in the clinic (but not for research) reached consensus in Round 3. Ultrasound failed to reach consensus for either.

**Conclusion**

Consensus was reached that 9 of the 11 technologies identified could aid OA subcategorisation. Interestingly, these 9 are the more recent and rapidly evolving technologies (unlike non-consensus-reaching X-ray and ultrasound), suggesting further improvements are likely.

**Keywords (4-6 words).**

Subcategorisation, technology, Delphi process, osteoarthritis.

**INTRODUCTION**

It is predicted that there will be a 4- to 6-fold increase in the number of total joint replacements for osteoarthritis (OA) in the coming decades(Ryd). Despite the increase in prevalence and the large body of literature existing on the subject, definitions of OA, whether in clinical or research environments, are often disparate. Re-defining OA and sharpening definitions could help bridge the gap between research and the clinic, and perhaps the advent of recent technological advances could enable better subcategorisation of this disease. This in turn may render existing treatments more effective if applied to selected or stratified subgroups and, indeed, other subcategories of patients may be found who might be better suited to new treatments.

OA has traditionally been subcategorised using technology, particularly X-rays, for more than 20 years. However, more recently there have been many technological developments, for example in genomics and other ‘omics’, different forms of imaging, computational analysis and big data management. The OATech Network+ organised a Delphi focus meeting on the application of technology to improve OA subcategorisation. The meeting commenced with experts in the fields of engineering, rheumatology, orthopaedic surgery, radiology, physiotherapy, biology and OA pain perception sharing their expertise of what OA represents to them. Experts in the more recently developed technologies subsequently provided summaries on their application to OA allowing discussion on how they might help with subcategorising OA. A summary of these is reported below.

**Genetics and genomics**

The field of complex trait genetics has witnessed a revolution in technological advances over the last decade, enabling the genome-wide interrogation of sequence variation, leading to the discovery of thousands of genetic risk loci. Recent methodological advances have now also enabled deep molecular characterisation of disease-relevant tissues collected from primary patients, or studied in cellular and organismal models of disease. Together, these approaches can help enhance our understanding of the mechanisms underlying disease development and progression(Zengini 2018). Large-scale genetics can help improve our understanding of the genetic aetiology of OA and related subgroups by leveraging big data in genetics, genomics and medically-relevant phenotypes from rich epidemiological resources, patient collections and disease registries. Functional genomic approaches for integrated molecular phenotyping of relevant cell types can help translate insights from genomics into mechanisms of disease in order to overcome the critical barrier of there being currently no disease-modifying treatment for OA. The relevant tissues for OA are readily available at joint replacement surgery, enabling the study of molecular processes in the appropriate tissues, both to fill a gap in our fundamental understanding of biology and to identify novel therapeutic avenues.

**Epigenetics and Functional Analysis**

Epigenetics is a mechanism used by the cell, tissue and organ to regulate gene expression in a dynamic manner by reversible chemical changes to the genome. There are three epigenetic markers: DNA methylation, histone modification and the activity of regulatory RNAs(Barter 2017). Epigenetic changes are context specific and show temporal and spatial effects. They act during skeletogenesis and joint formation, and also have a role in OA(Barter, Reynard, Van Meurs). As for genomic studies, joint tissues (eg cartilage, synovium or bone) are readily available in relatively large quantities to extract DNA, chromatin and RNA for epigenetic analysis. Such studies have led to subcategorisation of OA by, for example, identifying individuals who have an inflammatory component to their disease (Reynard).

**Proteomics and Metabolomics**

Proteomics and metabolomics can both be used to identify molecules that may be predictors of early disease, disease progression response to treatment, as well as identifying potential treatment targets by interrogating synovial fluid, serum or plasma, cells, secretomes and whole tissues with each platform. Synovial fluid not only contains systemic protein or metabolite markers of disease, but due to its proximity to numerous tissues which are primarily altered during OA, it holds significant potential for the discovery of proteins and metabolites to aid subcategorisation of the disease.

Whilst transcriptomics can indicate to the proteome, the relationship between mRNA and proteins varies and thus identifying proteins in a sample and how they vary is paramount. Quantitative proteomic differences between sample groups can be identified using either absolute or relative quantification and with or without labelling (reviewed(Wong 2010)). Absolute quantification has been used to measure up to 20 targeted proteins in a single experiment(Cox 2005, Peffers 2013). Label-free relative quantification using synovial fluid has also been used(Peffers 2015) and predictors of treatment outcome with autologous chondrocyte implantation (ACI) have been investigated for a number of biomarkers. Degradomics is another proteomic method that may be useful in OA subgrouping, assessing cleavage products at different stages in OA(Peffers 2017). A further development, Matrix Assisted Laser Desorption Ionization Mass Spectrometry Imaging (MALDI-IMS), has been used to identify proteins and neopeptides altered in cartilage ageing and OA (Peffers 2014).

**Molecular signatures and biomarkers**

All of the techniques described above (genomics, epigenomics, proteomics etc) can assist in the search for biomarkers in OA, in terms of the “Burden of disease, Investigative, Prognostic, Efficacy of intervention and Diagnostic (BIPED)” classification scheme(Kraus 2015). To date, many candidate proteins, carbohydrates and lipids(Watt 2016) have been investigated(Watt 2018). Several are associated with disease progression in OA cohorts, but are not able to stratify individuals(Kraus 2017). A ‘molecular signature’ representing multiple protein or non-protein markers may be more realistic for OA than finding a single biomarker, perhaps indicating relevant mechanisms within the disease.

Although singleplex antibody-based assays remain the mainstay for investigation of candidate protein biomarkers, multiplexing with higher sensitivity and specificity for complex biological fluids, are now possible by proprietary adaptive immunoassay approaches, such as electrochemiluminescence or proximity extension assays (combining antibody and PCR technology) (Soul 2018). Immunoassay or mass cytometry (e.g. CyTOF), antibodies limit the absolute number and combinations possible, whereas non-antibody approaches circumvent these issues. Modified aptameric assays (aptamers being short sequences of nucleotides which are selected for their specificity to bind proteins in much the same way as an antibody) can be multiplexed to quantify thousands of proteins simultaneously in a single sample. These approaches have the ability to identify molecular endotypes or predict drug toxicity.

**Clinical Engineering**

The International Classification of Functioning, Disability and Health (ICF) provides a framework for understanding disability which links the body functions and structures to activity and participation. Clinical movement analysis, in particular 3D gait analysis, allows clinicians to measure the impact of arthritis on walking. This is important as patients often perceive their walking pattern as a cause as well as a consequence of the disease, particularly in the spread to other joints. Patients with unilateral disease do often go on to develop bilateral symptoms(Metcalfe 2012).

Previous work(Metcalfe 2017) has described gait in patients with single joint disease (one knee only), who do not have a typically antalgic gait pattern, but have knee loading which is high throughout the stance phase, giving them a high moment impulse, combined with muscular co-contraction. This co-contraction, measured using electromyography (EMG) further increases contact forces in the joint. 3D gait analysis can detect bilateral overloading in both hip and knee joints in patients with unilateral, single joint disease. The adopted tentative gait pattern seems to be a risky strategy for the health of the other joints.

Whilst knee pain and loading measures improve after knee arthroplasty, some patients improved more than others and abnormal loading patterns often persisted(Metcalfe 2017). 3D gait analysis is useful in understanding the control and loading of the joints during movement and appreciating these changes in gait is important in providing appropriate therapies, such as bracing or biofeedback.

In knee OA populations biomechanical measures at baseline have also been used to predict radiographic disease progression(Miyazaki 2002), future total knee arthroplasty (TKA)(Hatfield 2011) and stratify response to interventions such as and lateral wedge insoles(Arnold 2016) and TKA(Metcalfe 2017).

**Activity monitoring**

Recent OARSI guidelines have also advocated the use of activity monitoring devices to collect objective measures of physical activity (Dobson et al 2013). It is important for individuals with OA to remain physically active, with evidence that physical activity can reduce OA related pain(Fransen 2015), as well as increasing muscle strength, joint range of motion and cardiovascular fitness. Technology is rapidly advancing in terms of the measures and accuracy which activity monitors can provide. Activity monitoring for subgrouping of OA requires large amounts of data and smart phones and wearable technology now offer the potential to collect this data.

**Machine Learning and ‘Big Data’**

Much of the technology described with potential to improve OA stratification creates very large data sets which require computational analysis; as the level of data increases, meaningful analysis becomes more challenging. The use of complex artificial neural network architectures or machine learning (ML) and modelling have been shown capable of representing and learning predictable relationships in many diverse forms of data. These computational tools hold promise for transforming the future of ‘omics’ and other technologies which acquire huge data sets(jamshidi 2019) or Big Data.

 Imaging modalities such as MRI, with each set of images containing vast amounts of information, are used as clinical diagnostic tools but lend themselves well to analysis via ML. For example, ML has been used to develop an automated method for grading degeneration in the spine and intervertebral disc on MRIs(Jamaludin 2017, Jamaludin/Kadir 2017), such as are used in the Pfirrmann Score(Pfirrmann et al 2001) for degenerative disc disease or OA of the spine (developed as ‘SpineNet’). The system can robustly extract measurements for this, in addition to having the potential to identify other phenotypes such as spinal stenosis or ‘Modic’ changes in the vertebral endplates. This approach, as with other technologies acquiring Big Data, requires well defined cohorts of patients, both for developing the program and then subsequently a further cohort for validation. SpineNet also has the capability of producing so-called ‘Hotspots’ or saliency images that can be used to visualize the parts of the MRI that are the likely source of the output, so possibly defining completely new phenotypes from this unbiased approach.

A prerequisite for imaging biomarker discovery is the extraction of robust and discriminative radiological measurements from degenerated joint MRIs, although the lack of imaging biomarker standardisation within the research community and the inherent intra- and inter-reader variability has hampered research to date. Machine learning in the form of computational analysis and the development of automated programs, can offer a robust, repeatable and rapid way to analyse large cohorts of MRI images, or any other form of potential biomarker. The ability to handle large data sets i.e. from MRI or genomics studies will be an important tool in the identification of OA biomarkers and phenotypes.

The technologies mentioned above have developed rapidly in the last decade. For example, a literature search for ‘genomics’ or ‘epigenomics’ (using Medline and Embase) over the last 30 years highlights the increased awareness and use of such technology. From 1990-1999 gemomics or epigenomics shows a total of 10 publications, 2000-2009 shows 7,322 and 2010-2019 shows 23,426. With the rapid development of these technologies, it seemed appropriate that the OATech Network+ should address the topic of the potential of technologies for subgrouping OA and it was felt that a Delphi meeting would be an appropriate approach.

**METHODS**

This Delphi study consisted of a two-day focus group meeting, together with online surveys, to assess the level of agreement on a number of statements relating to OA and the use of different technologies. The group consisted of orthopaedic surgeons, rheumatologists, radiologists, engineers, clinical engineers, veterinary and research scientists and physiotherapists, all with expertise and significant interest in OA. A questionnaire was formulated based on the most widely used technologies and research tools which may aid subcategorisation of OA. In addition, selected examples of OA categorisations were taken from the recent literature through primary searches (using Medline, EMBASE and PubMed with ‘definition of osteoarthritis’ as a search term) and articles known to the authors. Questions which required the members of the Delphi panel to provide free-text opinions were also included in the questionnaire. For example, participants were asked to provide a statement detailing their personal definition of OA. Answers to this question were then used as a starting point for discussion at the meeting and to make sure all panel members had a similar definition and understanding of OA.

The questionnaire was tested on world leading experts in the field of OA and modified slightly on their advice, before being distributed electronically to the Delphi panel over 3 rounds. Each panel member was asked if they agreed/disagreed with each of the statements. Round 1 was completed before the 2 day meeting. Talks were given at the start of the meeting by experts in the technologies presented in the Introduction. All statements in Round 1 were retained for Round 2, which was completed at the end of the first day of the meeting, to assess the impact of the expert talks on the opinions of the Delphi panel. Day 2 of the meeting involved a whole group discussion on the Delphi and the results from Rounds 1 and 2. Round 3 was completed at the end of day 2. Expert consensus was reached for each statement when ≥80% participants agreed with the statement and rejected if ≤20% of participants agreed, as used in previous Delphi studies(zhang 2008).

**Participant identification and inclusion**

Experts were selected from a wide range of representative disciplines relevant to the field of OA. All 130 members of the OATech Network+ were invited to take part. The Delphi questionnaire was emailed to 36 potential Delphi panel experts who were all active in the OA field and expressed an interest in attending the meeting.

All invited experts who completed Round 1 and attended the two day meeting were included in the study as Delphi participants. If the participant did not complete Round 1 and 2 of the Delphi or did not attend the meeting, they were excluded from the third round and their results from Round 1 and 2 were not used.

**RESULTS**

Thirty three experts responded and completed the questionnaires, so becoming the members of the Delphi panel. This consisted of 13 basic science researchers (including 2 PhD students), 2 orthopaedic surgeons (including 1 PhD student), 3 physiotherapists, 4 rheumatologists, 7 engineers, 2 radiologists, 1 veterinary researcher and 1 clinical efficacy researcher from the UK (n=31), America (n=1) and the Netherlands (n=1). However, several members were multi-faceted, for example, one individual may be clinically active, performing basic science research and running clinical trials. The questionnaire showed 37% of the panel members were actively treating patients, whilst 63% were not, but might have patient contact. Twenty seven percent of panel members had been working in the field of OA for 0-5 years, with twenty four percent being involved for >20 years (figure 1).

The wording in the statements and the results of the Delphi questionnaire over 3 rounds are shown in Table 1 and summaries of the definitions of OA provided by participants from different disciplines in Table 2. Not all panellists answered the question on defining OA, so results are shown from those available, with only small variations between and within professions.

None of the six categorisations of OA taken from recent literature reached consensus in any round. Furthermore, 4 of the 6 literature-derived definitions demonstrated a decrease in agreement between Rounds 2 and 3 (following the face-to-face meeting).

There was unanimous agreement in Rounds 1 & 2 that the latest technological advances could be used to improve OA subcategorisation. Of the technologies identified, only the statement ‘X-rays alone can be used to categorise OA phenotype’ failed to reach consensus in rounds 1 and 2, whilst there was no consensus in Round 2 for either X-rays or ultrasound as technologies which would to improve clinical OA subcategorisation (Table 1).

The technologies which gained greatest consensus in Round 2 for being of use in improving subcategorisation of OA were: machine learning (100%), genetic analysis and MRI (both 97%), proteomics and wet biomarker analysis (both 93.8%), activity monitoring (90.9%), metabolomics (both 90.6%), epigenomics and clinical engineering (both 88%). Eighty three percent of participants thought X-rays could aid subcategorisation of OA in Round 1, but this reduced to 49% in Round 2, whilst for ultrasound this changed from 59% in Round 1 to 67% in Round 2. Ultrasound was described as useful for identifying inflammation in the knee and could therefore be valuable in subcategorising OA, although some members did not feel educated enough to make an informed decision as it was not one of the technologies presented at the meeting. There was much discussion on the usefulness of X-rays and the commonly used Kellgren-Lawrence (KL) score. Discussions highlighted that it is considered outdated and flawed but that X-rays are still very useful in diagnosing and assessing OA in the clinic, for example, for suitability for arthroplasty.

**DISCUSSION**

Whilst OA has long been recognised as a heterogeneous multi-faceted disorder, progress into defining subgroups or categories has been poor; this is a likely reason why several clinical trials of novel pharmaceuticals or Disease Modifying Osteoarthritis Drugs (DMOADs) have failed (Hellio 2013, Kardsal 2015). In other areas of medicine such as asthma, subgrouping has been achieved according to the pathological mechanisms (sometimes referred to as molecular endotyping) and clinical phenotyping (Svenningsen 2017). It is to be hoped that this can be achieved for OA, which could result in improved diagnosis, understanding of disease mechanisms, identification of novel therapeutic targets, the development of new therapies and, subsequently, improved treatment of patients. Indeed this was a conclusion of the inaugural meeting of an EPSRC-funded UK initiative for OATech Network+, with the subsequent decision to utilise a Delphi process to address this topic. Our Delphi study further highlighted the lack of robust, overarching definitions of OA that are applicable across the various fields as there was variation in the definitions of OA provided by individual panel members. This was further emphasised by the absence of expert agreement with current OA categorisations in the literature.  This result aligns with other studies that have highlighted the urgent need for updated definitions and categories (Kraus 2015, Kingsbury 2016).

The ultimate aims of this primarily UK-based Delphi study were to determine, using a panel of experts, 1. whether existing technologies could aid in the subcategorisation of patients with osteoarthritis (OA) and 2. whether there is good knowledge and awareness of these technologies. Machine learning, genetic analysis, MRI, proteomics, wet biomarker analysis, activity monitoring, metabolomics, epigenomics and clinical engineering were all agreed upon by the panel to have the potential to improve the subcategorisation of OA. However, not all the expert panel had been fully aware of their potential.

One of the technologies resulting in considerable discussion was X-rays and the KL scoring system. Discussions led by orthopaedic surgeons highlighted that whilst the KL is flawed and outdated, X-rays remain a useful technology clinically. Whilst MRIs give better detail and OA diagnosis, X-rays are routinely used to aid clinical decisions, being cheap and readily available, e.g. on the need for arthroplasty.  If a better scoring system could be designed and broadly adopted, it could be of great benefit in the OA field for research as well as in the clinic.  The KL radiographic classification scheme for OA, first described in 1957(Kellgren 1957), remains the most widely used clinical tool for the radiographic diagnosis of OA(Braun 2012, Kohn 2016), despite its known limitations, such as assuming a linear radiographic OA progression and being insensitive to change(Braun 2012). However, using machine learning and neural networks to analyse plain radiographs, produced promising results, even when based on the KL system(Tiulpin 2018, Norman 2018)with a focus on autonomy and an unbiased approach.  It is anticipated that the further use of machine learning and artificial intelligence may yield an improved and consistent scoring system in the near future.  KL needs standardising for both clinical and research purposes and improved sensitivity would aid research further, possibly by allowing the identification of OA subgroups.

Whilst 8 other technologies reached consensus as being useful, machine learning was the only technology to receive 100% consensus in its ability to improve OA subcategorisation in Round 2 of the Delphi, highlighting recognition of its potential for use in the OA field.  In big data science, machine learning is based on computer algorithms that can learn to identify complex patterns based on real data (Kononenko 2001, Lane 2012). The goal of machine learning is to enable an algorithm to learn from past and/or present data and then to make predictions or decisions for unknown future events (Landset 2015).

Another field to which machine learning and artificial intelligence will be of paramount importance due to the generation of ‘big data’ is genomics.  The advances in molecular technologies in recent years have not only transformed opportunities for successful biomarker and molecular signature discovery in OA. As with other technologies already described, integration with advanced analytical approaches, including machine learning and or artificial intelligence, provides the ability to build and test complex models incorporating important non-biomarker covariates.  Multi-omics data has been able to generate biomarkers that have allowed the division of patients into subgroups e.g. in oncology and other chronic diseases such as asthma(Lin et al 2009). Patients were able to be subcategorised into groups based on genetic variability and other biomarkers so that medications may be tailored to individuals (Lin et al 2012, Lin et al 2006). With big advances in multi-omics approaches such as genomics, proteomics, metabolomics and epigenomics, the sheer amount of data generated by these technologies is challenging.  In addition, roadblocks remain to overcome our understanding of all the interactions and functions of the genome.

Innovative approaches using machine learning/artificial intelligence should improve our understanding of disease via functional analyses and so potentially reveal patient subgroups. For example, ML/AI could help in a more comprehensive analysis of epigenetics, which is of great value in understanding the interplay between the genome, the cellular environment and the progression of disease.

Epigenetic changes can modulate the impact of risk-conferring alleles of DNA polymorphisms that are associated with OA. For example, if a polymorphism is in a gene-regulatory element and the risk allele reduces gene expression, its effect can be attenuated or aggravated by DNA methylation of that element in an allele-specific manner(Reynard 2017). As such, subgrouping OA patients by their genetic and epigenetic profile can reduce the heterogeneity seen across patients and can enhance the interpretability of functional studies of genetic risk.

Another technology which has categorized OA phenotypes is metabolomics. Two principle metabolomics platforms have been used: nuclear magnetic resonance (NMR) and mass spectrometry (MS). NMR metabolomics is non-destructive, quantitative, reproducible and cost effective. Both techniques have identified up to 32 differentially expressed metabolites in synovial fluid from OA and rheumatoid arthritis (Claire – needs a ref). Improved instrument and analytical capability will only lead to better subcategorization and stratification in the future.

Large datasets are also generated from activity tracking and are likely to provide further opportunities to aid the stratification of OA populations. Whilst research in the past has generally been limited to measuring activity for short durations (i.e. up to 7-days) pre or post-surgery with limited information being gathered, fitness trackers and smartphones have revolutionised the opportunities to collect continuous activity data with much more actual loading and activity data being gathered more reliably and over longer time periods. Objective measures of physical activity can be used for monitoring recovery e.g. following joint arthroplasty, to measure short term recovery in terms of daily step count change over the first four weeks post-surgery(Toogood 2018). Extending this approach over a large sample population would allow an expected trajectory of recovery to be developed such that patients deviating from it could, for example, be flagged for follow-up consultation. Similarly, studies have investigated longer term monitoring with follow-up measures taken at 3-12 months post-surgery(Jeldi 2017). Interestingly, there was no substantial increases in activity after 12-months, concluding that more behavioural interventions are required to promote physical activity in the recovery period.

This Delphi study also highlighted that the OA field has a real opportunity for discovery work to resolve unanswered big questions in this poorly understood disease, perhaps challenging some established but non-evidence based assumptions about the presence or absence of disease subcategories. The development of clinically meaningful subcategorisation of the disease that is amenable to both pre-clinical research and targeted intervention would appear achievable in the next 5 to 10 years. The wider use of existing technologies presented here which will only improve in capability and capacity in the near future will likely have a large impact on achieving this goal.

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**Author contributions**

**All authors contributed to the ideas, questionnaire and writing the manuscript. All authors gave final approval of the version submitted.**

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**Conflict of interest**

**The authors report that there is no conflict of interest.**

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**Figure legends**

**Figure 1.** Pie chart indicating how long the DELPHI panel members have been working in the field of OA.

**Figure 2.A.** Frequency histogram indicating the change of panel members’ response as to whether different technologies were able to improve OA stratification in Round 1 (before the focus meeting) and Round 2 (after the instructive lectures at the start of the meeting). Nine of the 11 technologies reached consensus after the 2nd round (shown in bold). B. The modified question related to X-ray and ultrasound technologies for the 3rd round for the clinic and research and the % agreement reached. The black horizontal line indicates the percentage needed to reach consensus.

**Table 1.** Statements used in the DELPHI and the percentage of participants who agreed with the statements at each Round.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  **DELPHI statement/Question** | **Round 1** | **Round 2** | **Modified question for round 3** | **Round 3** |
| **Percentage agreement with statement** |
| 1 | OA is a disease of 1. Bone
2. Cartilage
3. **Bone and cartilage**
 | 1. 2.9
2. 5.7
3. **91.4**
 | 1. 3.1
2. 0
3. **96.9**
 |  |  |
| 2 | OA always involves other tissues in the joint in addition to bone and or cartilage | 63.9 | **87.9** | **OA involves other tissues in the joint in addition to bone and cartilage** | **100** |
| 3 | Early OA needs categorising differently to ‘established OA | **86.1** | **87.9** | Panel decided not to take this question forward |  |
| 4 | Osteoarthritis needs re-defining | 65.7 | 69.7 |  |  |
| **5** | **OA is a continuum** | **88.6** | **97** |  |  |
| **6** | **Subcategorising OA is useful** | **94.3** | **100** |  |  |
| 7 | The definition of OA needs to be joint specific | 55.6 | 69.7 | The definition of OA needs to encompass joint specific differences | 66.7 |
| 8 | OA phenotypes should rely on underlying mechanisms | 73.5 | **84.8** |  |  |
| 9 | X-rays alone can be used to categorise OA phenotype | 5.6 | 6.1 |  |  |
| 10 | The Kellgren-Lawrence (KL) is the most appropriate for categorising OA on X-ray | 50 | 74.2 | **There is a need for an improved scoring system than the Kellgren-Lawrence for X-rays** | **93.9** |
| 11 | MRI has no role to play in categorising OA | 2.8 | 9.1 |  |  |
| 12 | A universal OA categorisation system can be used for all clinical cases of OA | 44.4 | 56.3 | Panel decided not to take this question forward |  |
| 13 | The same categorisation system for OA can be used in the clinic and or research studies | 57.1 | 59.4 | The same categorisation system for OA should be used in the clinic and or research studies | 78.8 |
| **14** | **The latest technological advances can be used to improve OA subcategorisation** | **100** | **100** |  |  |
| 15 | Please say if you agree or disagree that the application of the following technologies can improve clinical OA subcategorisation***Epigenomics******Genetic analysis******MRI****X-ray**Ultrasound****Metabolomics******Proteomics******Wet biomarker analysis******Machine learning (AI)******Activity monitoring******Clinical engineering*** | **84.8****91.4****100****82.9**58.878.8**87.9****97.1****88.9**68.672.2 | **87.5****97****97**48.566.7**90.6****93.8****93.8****100****90.9****87.5** |  | Clinical**87.9**75.8 | Research75.869.7 |
| 16 | Different OA subcategorisation systems have been suggested in the literature recently. Please say if you agree or disagree with the following statements taken from the literature.1. Examples of OA can be: Hip/knee/hip and or knee (Hackinger et al 2017).
2. Pain, symptoms, clinical examination and X-rays are the most useful factors in diagnosing early OA(Luyten et al 2018).
3. Pain, psychological distress, radiographic severity, BMI, muscle strength, inflammation and comorbidities are all associated with clinically distinct OA phenotypes.

(Deveza et al 2017).1. Minimal joint disease, malaligned, biochemical, chronic pain, inflammatory metabolic syndrome and bone and cartilage metabolism are all main phenotypes of OA.(Dell’Isola et al 2018).
2. Knee OA phenotype is defined by patient reported frequent knee pain, cartilage damage and the presence of degenerative meniscal tissue.

(Pihl et al 2017).1. OA can be classified by symptomatic radiographic OA (primary criteria) and pain alone (secondary criterion).
 | 58.345.76061.858.831.4 | 72.736.469.772.748.524.2 |  | 51.542.451.548.539.436.4 |

**Table 2.** Definitions of OA from different professions on the Delphi panel.

|  |  |
| --- | --- |
| **Profession** | **OA definition** |
| Physiotherapists | A syndrome affecting the joints of the body |
| Joint pathology leading to pain and functional limitation that involves genetics and epigenetic factors |
| Rheumatologists | Structural alteration of cartilage and bone in a joint which results in pain and loss of function |
| A disease of the whole joint with distinct clinical and structural phenotypes |
| A disease of many tissues of the joint including cartilage and bone, associated with pain or stiffness |
| Osteoarthritis is a whole-joint disease, affecting articular and periarticular tissues. It has components of degeneration, regeneration and low-grade inflammation that differ in extent and clinical consequences between joints, disease stages and patients |
| Orthopaedic Surgeons | Structural and biological derangement of joint (that isn’t rheumatoid/ankylosing spondylosis/psoriatic |
| A painful condition involving changes in multiple tissues of the joint |
| Engineers | A disease of the joint, characterised by pain, loss of function and degeneration/progressive damage of structures in/around the joint |
| Musculoskeletal disease possibly triggered by altered joint biomechanics and biological signalling leading to joint tissue degeneration, inflammation and pain |
| Radiologist | Degenerative joint change currently based on exclusion of other causes |
| Vet | Degenerative whole joint disease with an inflammatory component |
| Scientists (researcher) | Joint disease that results in cartilage degeneration, bone changes and pain |
| Degenerative disorder of the joint |
| A degenerative disease of the bone and cartilage. Can lead to cartilage loss, joint inflammation, changes in the bone and pain |

**Figures**



**Figure 1.** Pie chart indicating how long the DELPHI panel members have been working in the field of OA.



**Figure 2.A.** Frequency histogram indicating change of panel members’ response as to whether different technologies were able to improve OA stratification in Round 1 (before the focus meeting) and Round 2 (after the instructive lectures at the start of the meeting). Nine of the 11 technologies reached consensus after the 2nd round. B. The modified question related to X-ray and ultrasound technologies for the 3rd round for the clinic and research and the % agreement reached. The black horizontal line indicates the percentage needed to reach consensus.