Introduction

One of the most pressing needs in the health field is to treat the right patients with the right medicine. However, in light of the current complete lack of structure modifying treatments for osteoarthritis (OA), the even more pressing issue is to identify the optimal patient population in which to test a given treatment. For both economic and ethical reasons, identification of the optimal treatment for each individual patient is a pressing concern, not only for the patients and their physician, but also health care payers and the pharmaceutical industry. In the field of osteoarthritis (OA) this is of particular relevance, due to the heterogeneity of the disease and the very large number of affected individuals. There is a need to pair the right patients with the right therapeutic modes of action. At present, the clinical trial failures in OA may be a consequence of both bona fide treatment failures and trial failures due to clinical design deficiencies. Tools are needed for characterization and segregation of patients with OA. Key lessons may be learned from advances with another form of arthritis, namely rheumatoid arthritis (RA).

Personalized health care (PHC) may be more advantageous for a number of specific indications which are characterized by costly therapy, low response rates and significant problems associated with trial and error prescription, including the risk of serious side effects. We discuss the use of diagnostic practices guiding RA treatment, which may serve as a source of key insights for diagnostic practices in OA. We discuss the emerging concept of PHC, and outline the opportunities and current successes and failures in the OA field of polygenic disease are few. This poses the question of whether therapeutic areas and specific diseases outside the field of oncology can ultimately benefit from a tailored approach to therapy. It seems likely that certain therapeutic areas may ultimately prove more amenable to the application of PHC than others; these would be characterized by...

Which diseases are optimal candidates for personalized health care (PHC) and what drives the need?

PHC has often been suggested as a solution to this complexity, but the majority of examples of successful PHC are currently drawn from oncology and, as such, reflect a relatively simplistic concept of therapeutic stratification based on the targeting of constitutively activated pathways in an oligogenic model of disease. In contrast, reportable successes for PHC in the field of polygenic disease are few. This poses the question of whether therapeutic areas and specific diseases outside the field of oncology can ultimately benefit from a tailored approach to therapy. It seems likely that certain therapeutic areas may ultimately prove more amenable to the application of PHC than others; these would be characterized by...

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highly heterogeneous patient populations, low response rates and significant disadvantages stemming from stochastic ‘trial and error’ prescribing that increases risk of adverse events and economic burden due to exploratory prescriptions of high cost therapies.

Contrasting examples of the utility of a PHC paradigm are provided by osteoporosis and non-small-cell lung carcinoma (NSCLC). In osteoporosis, the need for stratification of patients is limited due to the relatively benign side effect profile and high response rates of established therapies\textsuperscript{2–4}, and the limited complexity of the disease involving mainly one tissue, bone. Despite early reports linking the commonly prescribed bisphosphonate therapies with stratified responses in terms of bone mineralization\textsuperscript{5}, novel clinical diagnostics have neither been extensively sought nor established, and therapeutic practice remains solely based on prognostic investigation. In contrast, following the initial characterization of a number of mutations that drive and maintain tumorgenesis\textsuperscript{6}, diagnostic practice for NSCLC has rapidly extended beyond classical pathology; physicians now have an opportunity to target highly effective therapies against signaling pathways activated by these mutations.

For the current discussion, we identified four major drivers of PHC.

- Identification of patients that are in greatest need of treatment
- Identification of the patients whom may respond optimally, with the highest efficacy and lowest safety concerns, to a given treatment
- Development strategy for a selected subpopulation of patients
- Efficient use of health care resources.

Although PHC might seem to be a highly attractive ‘magic bullet’ for patients, physicians, and payers, the interaction of several key considerations dictates the ultimate level of attractiveness of a PHC strategy. On the one hand, it is readily appreciated that the non-targeted treatment of a particular group of patients may not provide a cost-benefit-risk assessment that is adequately attractive [Fig. 1(A)]. In addition, it is equally readily apparent that restricting treatment to a diagnostically selected subpopulation with a high likelihood of a response may significantly and drastically improve this assessment [Fig. 1(B)], whereas another selected treatment more appropriate targets other patients [Fig. 1(C)], in contrast to the worst-case scenario in which only non-responders and Serious adverse events (SAEs) are the result of treatment.

Given the central precept that treatment of non-responders with a therapy associated with considerable side effects and costs will only provide risk without benefit to patients and waste scarce health care resources, it would seem intuitive that treatments delivering low response rates and a high potential for side effects would have the most to gain from PHC. Identification of non-responders will be of particular concern if the adverse effects are considered irreversible. Ethical and economic considerations clearly drive the earlier identification of such non-responders in order to allow for selection of an alternative intervention.

The heterogeneity of the patient population — lessons learned from rheumatoid arthritis (RA)

Experience with PHC in the context of RA provides an instructive example of the potential possibilities for OA. RA is a chronic autoimmune disease characterized by poly-articular inflammation resulting in massive tissue destruction in the affected synovial joints. Due to fast progression of joint structural damage that may lead to complete disability in less than 10 years, some patients need to be treated aggressively\textsuperscript{7}, and precise guidelines from European league against rheumatology (EULAR) are provided for patient care for both synthetic and biological interventions\textsuperscript{8–11}. Methotrexate therapy (MTX), often in combination with corticosteroids, is the most commonly used Disease Modifying Anti-Rheumatic Drug (DMARD) regimen in RA\textsuperscript{12,13}. Upon inadequate response or intolerance to therapy, initiation of a biologic therapy is recommended\textsuperscript{14}. There are a growing number of approved biologic therapies for RA. Given such a battery of diverse therapeutic options available to rheumatologists, it is not surprising that clinical remission of RA, or at least low disease activity, is often the goal of therapy\textsuperscript{15,16}. However, the absolute performance of biological therapies in randomized controlled studies in patients who have failed initial DMARD therapy is very similar based on the standardized criteria established by the American College of Rheumatology (ACR) for 20% (ACR20), 50% (ACR50) and 70% (ACR75)
improvement in disease activity: namely 50–65% for ACR20, 20–45% for ACR50 and 10–25% for ACR70. These data reveal a heterogeneity of drug responses and point to a significant and remaining unmet need for alternative therapies for the substantial number of patients who fall short of attaining remission or low disease activity from current therapy. Given the exposure of these inadequately treated patients to the risk of adverse events, together with a considerable societal economic burden of unremitting disease and cost of therapy, a PHC approach to the treatment of RA is pursued aggressively. The success will require that the current seemingly random stochastic approach to RA therapy needs to be replaced by a mechanistic and predictive understanding of response.

The heterogeneity of the patient population is heavily debated in the OA; failures in clinical trials, have made it increasingly more evident that OA is not one disease but has different phenotypes. Although the OA field is still without efficacious treatments to validate this hypothesis, several subtypes have been identified that may warrant different treatment strategies. Those subtypes receiving the most attention currently include the following: metabolic OA (including obesity), traumatic OA (including joint malalignment), inflammation driven OA and subchondral bone turnover driven OA phenotypes. This may be illustrated schematically as shown in Fig. 2. If a particular therapy works in a subset of patients with a specific disease phenotype, the response rates will be low in the absence of patient selection. Consequently, targeting a particular disease phenotype with the etiologically appropriate therapy would be expected to result in far higher response rates.

PHC in RA: current understanding of possible technological advances

Presently there are few positive examples of PHC for RA. Seropositivity, the presence of autoantibodies to rheumatoid factor (RF) or anticyclic citrullinated peptide (anti-CCP) observed in around 80% of patients, is an example of one type of biomarker with a modest ability to predict response to Rituximab. Another approach to the identification of subgroups of therapeutic responders has been genetics based. RA has a strong, but complex genetic etiology illustrated by the identification of 31 risk loci in seropositive RA, a very strong genetic risk factor HLA-DRB1, and the group of alleles referred to as the shared epitope (SE). To date, candidate and genome wide approaches to the discovery of response genes have been taken for anti-Tumor necrosis factor (TNF) and tocilizumab interventions. While associations have been established, the predictive capability has so far been insufficient to have meaningful clinical application. Wang et al. reported that polymorphisms identified in a genome wide association scan (GWAS) each accounted for less than 2% of the variance observed with change in DAS28 response to tocilizumab. Thirdly, the production of antibodies against biologic therapies, such as to anti-TNF antagonists, has also been associated with waning of drug response. Lastly, a multi-marker panel approach using 12 different markers is being pursued by Crescendo. While this may be predictive at the group levels additional tailoring of the panel of markers and algorithm may be needed to provide a meaningful result in the clinical practice at the individual patient level. Models predicting low disease activity (DAS28 < 3.2) at 52 weeks, utilizing clinical data collected at 12 weeks, have been produced for etanercept, etanercept with MTX, and certolizumab pegol. These models require validation in an independent dataset and analysis against a non-anti-TNF therapy to determine if these models are predictive of response to a specific therapy. Even for RA it is too optimistic to suggest that the optimal marker combination and final selection of the right patient is present, exemplified by the discussion in the RA field “Forget personalized medicine and focus on abating disease activity”.

For biomarkers to be utilized in PHC they need to be readily measurable with an acceptable level of sensitivity and specificity, accessible and reportable to physicians within a clinically actionable timeframe. As suggested above, current standard practice for RA at best provides an ACR50 response rate of 20–45% in a
randomized controlled trial [Fig. 3(A)]. By excluding patients unlikely to respond to the treatment the response rate may be increased and a subset of patients will not be exposed unnecessarily [Fig. 3(B)]. Thus an optimal strategy will both ensure a significant increase in response rates, but will also allow for exclusion of those patients likely to have a serious treatment related side effect.

A range of technologies may assist the implementation of PHC. While such technologies must be technically robust, relatively inexpensive, and easily accessible and simple to use, they are not limited to the current generation of non-invasive biochemical markers. A type of molecular marker has been developed that can quantify the levels of tissue destruction associated with a progressing pathology34,35. In contrast to total protein measurements of established inflammatory biomarkers, such as interleukin (IL)-1, IL-6 and C-reactive protein (CRP), these new biomarkers rely on the measurement of specific, circulating tissue protein fragments generated by up-regulated, active proteolytic enzymes. As an example, the major extracellular matrix (ECM) proteins of connective tissue in joints are type I, II and III collagen. Matrix metallo protease (MMP)-mediated degradation of these collagens results in the generation of the specific biomarkers, e.g., C1M, C2M and C3M respectively36,38. Additional protein fingerprints are generated by distinct enzymatic processing of collagen or other ECM proteins represented by the e.g., products like CTX-I, ICTP, CTX-II, C2C, ARGS (aggrecan), FFGV (aggrecan), C4M (type IV collagen), C5M (type V collagen) and C6M (type VI collagen)1,39. The measurement of different degradation products of a protein may elucidate different and frequently opposing metabolic mechanisms. This concept is exemplified by e.g., products of metabolism of type I collagen like: PINP, CTX-I, C1M and ICTP – each of these products provides distinct and unique information. PINP is a pro-peptide released during protein synthesis and can be measured as a surrogate biomarker of both bone formation and fibrogenesis40,41. CTX-I is a widely used biomarker for Cathepsin K mediated destruction of type I collagen, reflecting bone resorption42. ICTP is a triple cross-linked carboxy-terminal telopeptide of type I collagen generated by MMP-activity, but destroyed by the activity of other proteases43. ICTP is mainly released from connective tissue turnover. Finally, C1M is also released by the action of MMP’s from the helical domain of type I collagen. These different products of type I collagen provide different and complementary information on tissue integrity and turnover even though they in essence are measures of the same protein, albeit in different ways.

What does this mean for the OA field?

The list of failures and limited successes in clinical development for OA is growing, and includes among others, Inducible nitric oxide synthase (iNOS), strontium ranelate, Calcitonin, MMP inhibitors, Cathepsin K inhibitors and bisphosphonates44–47. These disappointing results may in part be due to hypothesis failures but also a result of applying these therapies to non-selected patient populations. Figure 4 offers a very preliminary but possibly clinically meaningful and clinically feasible strategy for selecting OA patients. OA might be divided into at least three different subtypes based on the most active joint tissue at a particular stage of disease (bone, cartilage and inflamed synovium) or the tissue with the predominant manifestations in particular patient populations. As examples, Treatment 1 may target early cartilage pathology such as manifested in traumatic OA, with high protease activities in the articular cartilage such as MMP and aggrecanase activities. Treatment 2 would target both bone and cartilage involvement, such as manifested in postmenopausal generalized OA. Treatment 3 may target late stage inflammation driven OA. Clearly these three different subtypes of OA would require different interventions and diagnostic algorithms, and one treatment that may be successful in one patient population may fail in another.

Based on even this simplistic subdivision of patients groups, the following treatment scenarios might be suggested.

- Patient phenotype 1: Traumatic OA, in the early disease course most likely involving a high level of protease activity destroying the cartilage subsequent to cartilage injury. These patients might benefit from a protease inhibitor treatment.
- Patient phenotype 2: Generalized OA, with high turnover of bone and progression of cartilage damage characterized by an intimate relationship between bone and cartilage in the pathogenesis of OA. These patients may benefit from an anti-

Fig. 3. (A) Treatment of the entire patient population, without preselection of patients, resulting in 30% response rates; (B) Preselecting 50% of patients may result in a 60% response rate, thus drastically improving the cost-benefit and benefit-risk assessments. Importantly, PHC is of benefit for not only identifying those patients who will respond safely to treatment, but also those patients who should not be exposed to the drug. Thus, an optimal strategy will both ensure an enrichment of response rates, and lower adverse event rates through exclusion of patients from the treatment pool for whom the therapy poses a serious risk. Importantly, SAEs can and may also occur in selected patients, as illustrated by the “half-man” being a non-responder as well as subject to an SAE.
Do different phenotypes in OA represent different pathological stages and/or different phenotypes?

It is important to recognize that OA is far from a static disease, and represents very distinct characteristics during the various stages of disease progression, i.e., the above mentioned phenotypes may vary over time. The different phenotypes of OA most likely represent different disease subgroups; alternatively they may represent the predominant tissue pathology during a particular stage of disease. Optimal therapy may be considered the ability to detect and target each of these stages or subgroups of disease.

This approach underscores the need to better understand the multiple pathways that result in the common end stage we refer to as OA. While these delineations may overlap to some extent and be dependent on the time and stage of disease, the scenarios represent testable hypotheses that call for further research to validate and refine algorithms for clinically meaningful patient phenotyping.

Fig. 5. The present figure illustrates key drivers of the disease and their speculated impact on the rate of disease progression. These distinct drivers of disease may be highly OA stage dependent and overlap to some extent. The length of the line is considered the relative importance, as such the line is longer for hormonal than autoimmunity driven OA disease, and consequently autoimmunity may lead to joint failure faster than hormonal regulations. All cases of OA may be caused by a minor or major joint trauma; however the rate of progression may be driven and accelerated by different factors. These factors may describe different OA phenotypes, and these factors may also be applied as tools for PHC allowing early segregation of patient as compared to traditional clinical diagnosis of symptomatic OA. Note that this figure provides a working hypothesis (and is hypothetical) as we do not know whether genetic factors are more important leading to faster progression (shorter length of the line) than e.g., mecha-transduction.

of function of key proteins53; (4) Hormonal, representing an imbalance in the endocrine system that may result in loss of skeletal protections, as observed in some postmenopausal women54. (5) Metabolic, in which an unhealthy phenotype, such as obesity, may drive OA through adipokines21; and (6) Mecha-transduction, in which mechanical loading may drive a “wear and tear” effect. Importantly, some factors may predispose at individual stages to either slow or fast progression; these are discussed and outlined in Table I. Of key importance, the risk factors and analysis methods outlined in Table I, may optimally be used in combination rather than stand alone technologies, in which imaging [X-ray and magnetic resonance imaging (MRI)], standard demographic description, genetic and novel biomarkers together provide value to patients. Such combination of modalities, imaging, demographic and serological biomarkers has in a few clinical settings been shown to provide additional improvement in odds ratios for identification of i.e., progression55.

A few factors of relevance to the different type/stages of OA are given attention. The release of citrullinated fragments of different ECM proteins as well as intracellular proteins has been shown to act as autoantigens. To date, one such fragment, ViCm, has been identified and shown to predict radiographic joint disease progression in a subset of patients56. Genetic factors may also be of particular importance as GDF5 mutations57 have been shown to predispose to a lack of repair potential, which may be of paramount importance after traumatic injury. In addition, there are a long list of genes that are related to cartilage and bone metabolism such as Receptor activator of nuclear factor kappa-B ligand (RANK), RANK-L, Sclerostin, Cathepsin K, V-ATPase, CLC-7, MMP-9 and -2, that may influence the traumatic and high turnover stage of disease58,59. Further, our current understanding of OA suggests that inflammation may be a driver of disease albeit not an initiator of disease, as mutations in IL-1, predispose to inflammation and consequently fast progression in OA60. This would be consistent with the biology of IL-1 and IL-1 receptor in chondrocyte function and cartilage degradation61. In parallel to RA where early radiographic
damage in RA is a paramount predictor of later damage\cite{22}, a similar concept is applied to OA where different imaging modalities clearly may assist in delineating different phenotypes and progression\cite{55,63,64}. These combined highlighted modalities, in addition to the traditional risk factors; age, significant trauma, obesity, altered gait, altered biomechanics (for example, a varus or valgus deformity), and excessive loading on the affected joint\cite{65,66}, may be part of a proposition for PHC in OA.

One relevant example of PHC in OA may be found in the recent fibroblast growth factor (FGF)-18 studies. In a retrospective analysis of data from a clinical trial with Sprifermin (rhFGF18)\cite{21}, a combination of two SNPs in the IL1RN gene could be indicative of disease severity/progression as well as potential response to Sprifermin in defined genetic groups\cite{58}. Four groups of patients were identified and tested for a statistical association with change in cartilage thickness/volume (as measured by MRI) and WOMAC scores. Groups of patients stratified for the SNPs rs9005 and rs315952 showed better response to Sprifermin therapy in terms of cartilage volume\cite{58}. This stratification may be combined with serological technologies or other biomarkers such as described in Table 1 to further improve the prediction.

### Which technological advances may facilitate the advent of PHC for the OA field?

The OA field is somewhat behind the RA field, although also in the RA field stratified phenotype directed treatment is also still in development. This difference in the available toolbox, critical to the success of PHC, is most likely due to the current lack of successful intervention strategies in OA. This is further underscored by the almost accepted postulation in the OA field that novel treatments may more readily be identified and developed by identification of the right subpopulation of OA patients. Consequently, this discussion is reminiscent of the chicken and the egg discussion. However, with the emerging BIPED categorization and stratification of biochemical markers in the OA field\cite{69}, tools are beginning to be identified that may assist in the advent of PHC for OA. Different methodologies are being classified as reflecting Burden of disease (B), Investigative (I), Prognostic (P), Efficacy of intervention (E), Diagnostic (D) and Safety (S)\cite{69,70}. Of most importance for PHC would be Prognostic markers at baseline that could predict optimal responders and Safety markers. Table 1 lists some of the genetic risk factors identified in GWAS studies, biochemical markers, and imaging markers which may facilitate the establishment of a PHC paradigm in OA by helping to define optimal patient populations for specific interventions.

We suggest that there needs to be a focused effort on PHC that could be initiated in existing cohorts. PHC efforts could be grounded in analyses of markers such as those listed in Table 1, to identify patients most likely to respond to a particular treatment. In addition, in other fields, marker panels are emerging for specific organ toxicity, such as the acute kidney injury panel\cite{71}, which is in direct alignment with the suggestion of the “FDA critical path” that the efficacy marker of one pathology may be the safety marker of another\cite{1}. Such public efforts may assist in generating a better roadmap for drug development in the OA field, by identification of the OA patient in whom safety indicators are optimized. Such efforts should also provide quicker and safer decision making in drug development that are of paramount importance for pharmaceutical companies to commit the needed investments in later stage clinical development. These efforts are expected to further lower the investment barrier, allowing more optimal clinical trial design for critical POC studies allowing for trials with fewer patients and shorter trial durations to reach an objective decision point. The best biomarkers would improve success related to the following:

1. Identification of fast progressors
2. Identification of the optimal patients for a specific type of intervention
3. Enablement of phase II and III studies with fewer patients
4. Decreasing cost of trials
5. Minimizing drug-related adverse events
6. Potentially providing early confidence in mechanism of action
7. Surveillance for off-target effects

### Conclusion

In conclusion, experience to date suggests that most medicines need to be developed to target specific subpopulations. We propose that OA is a suitable candidate for the application of PHC. As novel technologies and advanced clinical chemistry approaches, such as protein fingerprints or other robust methodologies, become a reality, the feasibility of PHC increases. The ever increasing prospect of PHC offers hope for a better future for patients, physicians and payers.
Author contributions

All authors discuss the concept of the manuscript. MK drafted the first version. All authors edited and approved the final version of the manuscript.

Conflict of interests

MK, AC Bj, KH and CC are full time employees of Nordic Bioscience. A company engaged in the discovery and development of biochemical makers. MK and CC own stock in Nordic Bioscience. CL is a full time employee of Merck-Serono, a company engaged in the development of treatment for OA.

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