Defining FiTNEss for treatment for multiple myeloma

Improving the healthspan—the length of the lifespan spent free of disease—and prolonging the human lifespan in general are important objectives both in medicine and for society. The difference between lifespan and healthspan encompasses not only the influence of disease, but also of rapid physiological deterioration and its consequent risk of concomitant illness and polypharmacy, further augmenting physiological decompensation—frailty. Frailty is a functional term that refers to a decline in physiological function, leading to dependency, vulnerability to stressors, and a high risk of poor health-related outcomes (eg, metabolic disorders, infections, and cancer), which results in an increased risk of morbidity and mortality.[1] All degrees of frailty have been reported in up to two-thirds of people with multiple myeloma, with severe frailty in at least 40% of these individuals in some reports.[2] However, patients with frailty, which are a growing cohort in the population of patients with multiple myeloma, are frequently excluded from commercial clinical trials and academic studies; an exclusion that prevents such individuals from accessing the innovative treatments and precision medicine approaches that are improving outcomes for many younger and fitter patients. Understanding and breaking down the barriers to trial entry for individuals who are frail is a crucial need, as is identifying those at risk of not achieving the maximum benefit from treatment as a consequence of too much toxicity.

An integral aspect of identifying this vulnerable group of individuals is to define the physiological age and capacity of patients with multiple myeloma so as to better manage the symptoms of the disease and the side-effects of its treatment. The International Myeloma Working Group Frailty Score (IMWG FS) is a myeloma-adapted geriatric assessment clinical scoring system, which includes not only functional but also clinical assessments, and is regarded as the gold standard for geriatric assessment in multiple myeloma.[3] This score identifies the fit, intermediate-fit, and frail among older people with multiple myeloma, and retrospective application has shown that the intermediate-fit, and especially the frail, are more likely to stop therapy prematurely, suffer more toxic effects, and have shorter remissions and a shorter overall survival compared with the fit group. Because this scoring system is complex, it is difficult to apply in a busy clinic and has not yet been rigorously tested prospectively, or in individuals younger than 55 years. Other, simpler and more objective scoring systems, such as the modified IMWG FS[4] and the UK Myeloma Research Alliance Myeloma Risk Profile,[5] have been developed and identified similar risks groups. Despite evidence showing the prognostic potential of these clinically based scoring systems, no prospective evidence has shown their predictive capability, which limits adoption into clinical practice. Furthermore, no evidence exists to define the dynamic nature of these assessments, and whether they can successfully establish the disease overlay effect on functionality. In addition, emerging data suggests that individuals defined as frail using IMWG FS might, in fact, include a subgroup of patients at higher risk of poorer outcomes—the ultra-frail.

The UKMRA Myeloma XIV FiTNEss trial (NCT03720041) is a randomised, placebo-controlled trial that aims to define the predictive biomarker capability of IMWG FS.[6] This trial will enrol patients who are deemed ineligible for high-dose chemotherapy and autologous transplantation, and who will receive an all-oral combination of ixazomib, lenalidomide, and dexamethasone. This oral combination will be delivered at standard doses, modified only in response to toxic effects (reactive group), or an upfront dose-delivery modification on the basis of their IMWG FS (proactive group), to define the effect of the frailty score to direct drug dose delivery on intended therapy delivery, adverse

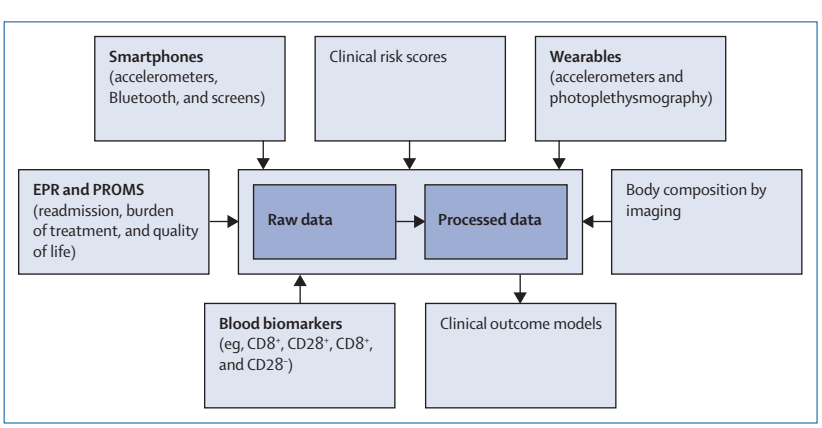

Figure: **Profilomics, embedding the host response biology in patient-centred ultra-stratification**
EPR=electronic patient record. PROMS=patient reported outcome measures.

events, and early mortality. The aim is to identify if the IMWG FS is predictive of outcome and can be used to direct care. The trial also aims to investigate whether doublet maintenance therapy (ixazomib plus lenalidomide) improves outcomes compared with single-agent lenalidomide without prohibitive toxic effects. Since recruitment began, between the first wave (ie, first and second quarters of 2020) and second wave (ie, third and fourth quarters of 2020) of the COVID-19 pandemic, the study has recruited more than 500 people for autologous transplantation (with a target of 740 people), with more than 40% of these individuals deemed as frail by the IMWG FS. The trial will test the dynamic nature of the geriatric assessment-based scoring system because the protocol will allow patients to either escalate or de-escalate treatment dosing as their IMWG FS changes with treatment and disease control, especially disease-related morbidity. In addition, the role of a combined IMWG FS and UKMRA strategy to define those at a very high risk (ultra-frail) of poorer outcomes will be established using this large trial dataset.

Due to the limitations of geriatric assessment-based clinical scoring systems, attention has turned to alternative biomarker development. These alternatives include laboratory assessments of senescent cell burden, such as immunosenescence, or evaluation of the senescence-associated secretory proteome.[2,7] Body composition assessment via imaging has also been presented as a key tool to identify individuals who are frail. The UKMRA Myeloma XIV FiTNEss trial will provide the bio-sampling platform (blood and imaging) to formally test and validate such biomarkers for the management of patients with newly diagnosed multiple myeloma. But a question remains: how can this information be used to formulate a personalised strategy for the care of older people with cancer? The answer might lie in the systematic data analysis of simultaneously measured variables, incorporating digital phenotypes to assess patient vulnerability using artificial intelligence as a delivery vehicle for Profilomics, embedding host response biology in patient-centred ultra-stratification (figure).

More research is required to personalise anti-cancer therapy to account for the biological consequences of accelerated ageing, and thus modify treatment delivery for optimal outcomes. FiTNEss is an important initial step, and will be key to improving the design of future clinical trials and how treatments are delivered in the clinic.

We declare no competing interests.

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