Introduction:
Cachexia is defined as a complex metabolic syndrome associated with underlying illness, characterized by loss of muscle with or without loss of fat. In cancer cachexia, reduction in muscle size has been demonstrated to be an independent risk factor for mortality. Loss of muscle in ICU patients is rapid and extensive and is also associated with mortality risk, but methods to measure muscle mass in these patients are lacking. Surrogate methods (DEXA, CT, ultrasound, total body water) do not measure muscle mass directly.

Methods:
The D3-creatine (D3-Cr) dilution method takes advantage of the fact that 98% of Cr is found in muscle and that muscle mass can be assessed by Cr pool size. Cr is transported into muscle against a concentration gradient and irreversibly converted to creatinine (Crn), which is excreted in urine. A single oral dose of D3-Cr is transported to skeletal muscle, and measurement of D3-Crn enrichment in a spot urine sample provides an accurate estimate of skeletal muscle mass.

Results:
The method has been validated in preclinical and clinical studies; in a large longitudinal observation study in older men, D3-Cr muscle mass was strongly associated with habitual walking speed, risk of falls, and incident mobility limitation; DEXA failed to show these relationships. The D3-Cr method is being used in a NICU study to measure changes in muscle mass in neonates (Gates Foundation Grant). Further, this method has been incorporated into a trial assessing the treatment effects of a ghrelin agonist in ICU patients with enteral feeding intolerance (NCT02784392). In this trial, the D3-Cr dose is delivered intravenously and a spot urine sample is collected at baseline and postdose.

Conclusion:
The D3-Cr method provides a non-invasive, accurate way to assess therapeutic agents that may mitigate the loss of skeletal muscle mass; it is of particular utility in clinical settings where changes in muscle mass are consequential, such as muscle loss during an ICU admission.