Patient's Body Composition in Oncology Trials:
A Case for Implementation

Hubert Beaumont[1], Catarina Ribeiro Alves[2], Antoine Iannessi[1], Jane Bentley[2]
[1]Median Technologies,[2] Syneos Health®

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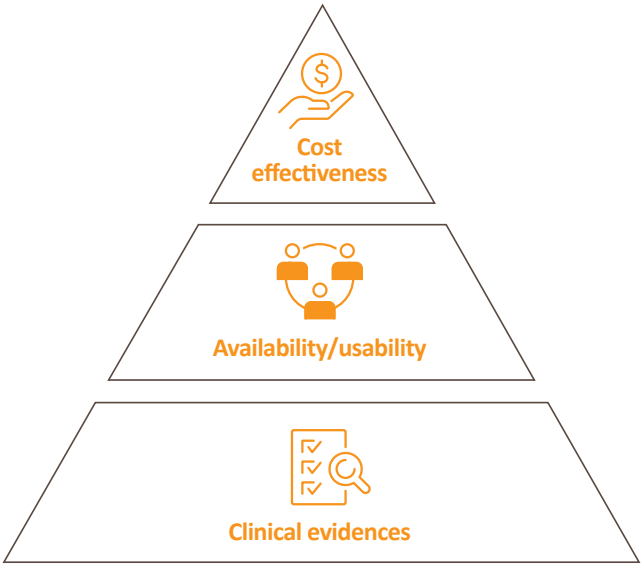
Introduction

During the past two decades, research about body composition has been growing exponentially. Since the early 60's, when skinfold thickness was the primary tool, an impressive variety of methods and systems have been proposed to evaluate body composition for diverse clinical applications.

A conservative definition of body composition refers to the characterization of the core anatomical components of a person's body, like fat (sub cutaneous adiposis (SA), visceral adiposis (VA)), muscle (skeletal and non-skeletal) and bones.

Despite the plurality of clinical applications and their huge promises, body composition assessments remain underused in clinical trials. The underlying reasons for the lack of incorporation of this novel biomarker in clinical research can be related to one or more of the following: level of evidence of clinical applications, availability of the systems allowing the assessments and practical adoption and cost effectiveness.



Overview of Clinical Applications

Health-related applications of body composition are diverse, from fitness, geriatrics, obesity screening, oncology and pharmacology (pharmacokinetics, dynamics and dosing).

Specifically in oncology, extensive research, including meta-analysis, show that body composition is key to improve prognostication and personalization of therapies[1][2], monitorization of patients under treatment[3] and also in clinical research to improve drug dosage and efficacy[4] [5].

Availability and Usability

Modalities

When implementing body composition measurements for clinical applications, the "how to" question rapidly arises. Many imaging methods are available, each featuring their own technical capabilities and challenges, Computed Tomography (CT) being currently the gold standard. Medical imaging offers different possibilities for quantifying body composition [6], mainly: Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Dual-energy Xray Absorptiometry (DXA).

Pros and cons of these modalities are well known:

— **CT** scans are faster, cheaper and more widely available but are ionizing;

— **MRI** is harmless but slower, more expensive and less available.

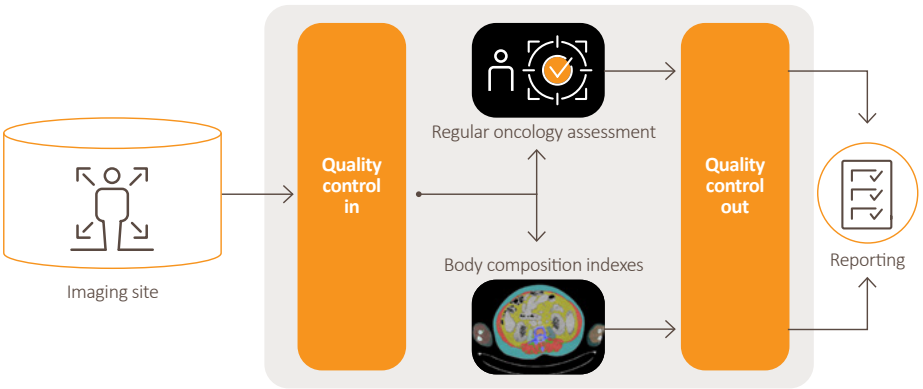
— Originally designed to evaluate bone mineral density, **DXA** is now a practical modality to assess bone mineral content (BMC), lean mass (LM) and fat mass (FM) but is less accurate than CT.

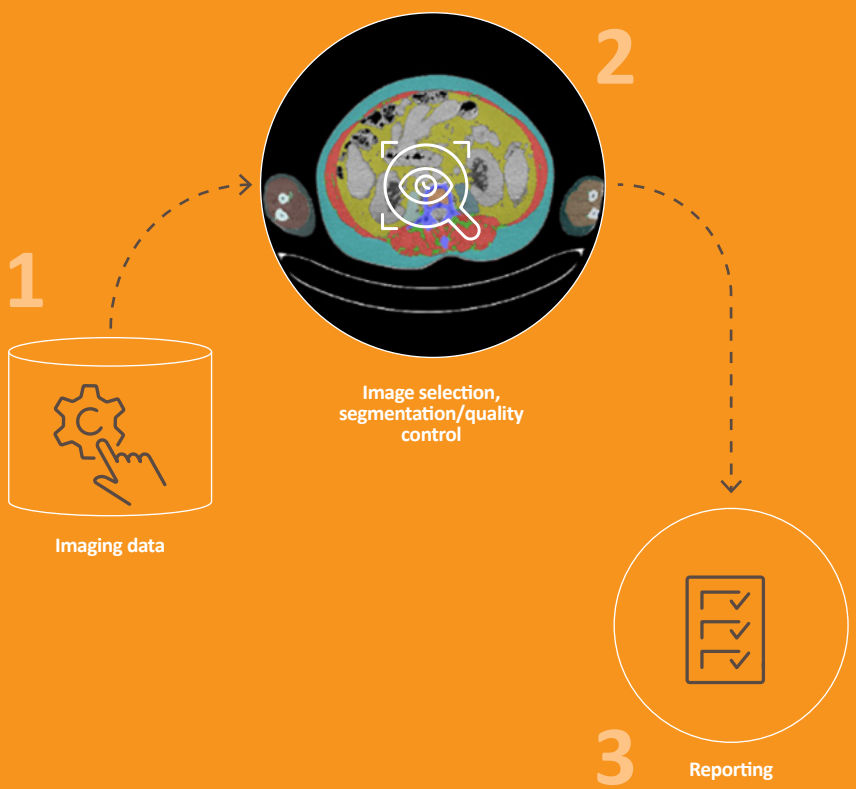
Oncology represents a unique field in this respect as cancer patients do CT scans routinely as part of their cancer diagnosis, staging and follow up. Therefore, the CT images are already available for these patients (without the need of an extra exam or additional radiation).

Integration in Workflow

The integration of body composition indexes, including the Skeletal Muscle Index, which are crucial for diagnosing sarcopenia, can be seamlessly incorporated into the workflow of oncologic trials. This approach is particularly feasible since these evaluations typically use standard body CT or MRI scans that are already part of such studies and clinical practice. By leveraging a dedicated core lab, the benefits of initial quality control (QC) during image acquisition can be maximized. The core lab can then perform image segmentation and analysis concurrently with ongoing oncologic assessments, without adding extra operational burdens. This process is facilitated by an automated system that is supervised by both a skilled technician and a radiologist, ensuring accuracy and efficiency in extracting body composition metrics.

Furthermore, assessing body composition has a faster turnaround time compared to traditional independent reviews. The iCRO (Imaging Contract Research Organization) team can manage this process internally, reducing the need for external independent experts. This streamlined approach not only expedites assessments but also enables the central determination of eligibility based on sarcopenia criteria, enhancing the efficiency of clinical trial workflows.





Technical Solutions

The assessment of body composition with imaging, for which evidence and technologies are widely available, relies on three steps: image selection, segmentation/quality control and reporting.

Standardization is key to reducing variability in this process. Similarly to standard oncologic reviews, a guideline for imaging acquisition and quality control is implemented to ensure that sites consistently provide correct and uniform images over time.

It is well-known that manual segmentation tasks exhibit high inter-reader variability. To address this, auto-segmentation algorithms [7] are utilized to control this variability. The analysis is supervised by a medical team and corrections, if necessary, are made by an imaging technician.

Cost-Efficiency of Assessing Body Composition in Clinical Trials

In oncology trials, it is estimated that approximately 10% of patient dropout is due to adverse events [8], and the cost of patient dropouts is significantly higher than that of recruitment. A conservative estimate places the cost of enrolling a patient in a clinical trial at $80,000 [9]. Therefore, improving patient retention represents a crucial opportunity for cost savings.

Drug dosage derived from body composition assessments creates an opportunity, as improved drug dosage could potentially reduce toxicities and hence reduce the rate of patient dropouts. (Can muscle health predict outcomes in clinical trials for oncology? January 31, 2023).

The cost effectiveness of using body composition can be estimated by comparing the cost of analyzing reliable body composition indexes to the savings made in avoiding a proportion of patient drop out.

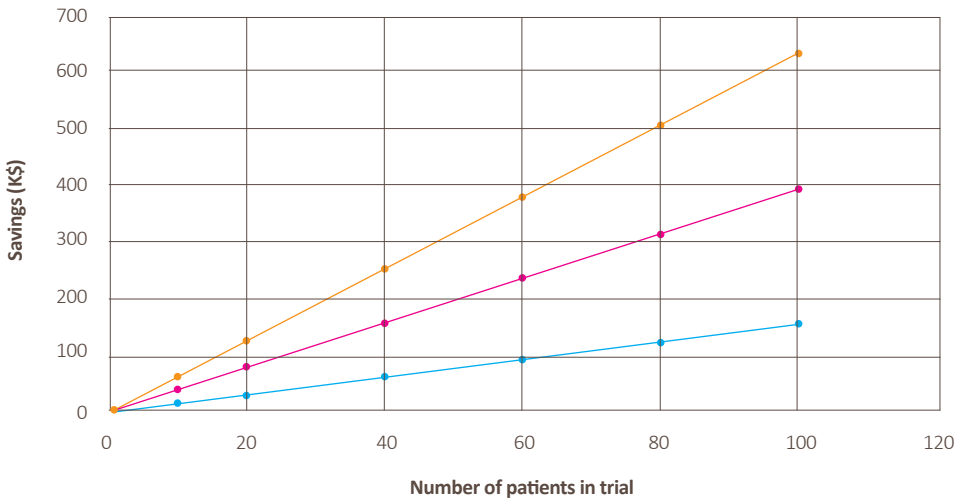
An evaluation of the cost of extracting body composition from CT scan images has been made by Cespedes et al. [10]: around 20' are required for manual segmentation of the 3 components Subcutaneous Adiposis (SA), Visceral Adiposis (VA) and muscle at L3 level, which corresponds to approximately 1 hour per patient (including segmentation, quality control and report). The technician and the radiologist are paid, on average, respectively 50$/h and 250$/h (salary.com, while a conservative estimate for the cost of an automatic segmentation is $50 per scan (<1 s/scan for neural networks [11]).

On the other hand, potential savings can be estimated based on an early sarcopenia study from Gu et al [12], which reports that sarcopenia can be detected using deep learning with an AUC of 0.874. This indicates that a significant proportion of "at-risk" patients can be identified early and managed appropriately, potentially reducing costs and improving outcomes.

Costs and savings of using body composition can be embedded in a simple cost-effectiveness model:

For a trial planning to recruit N patients with a 10% rate of dropout due to toxicity with a Cost of Dropout (CostDPout) per patient and a Cost of Segmenting Body Composition (CostSegBC) per patient, if the use of body composition for dosage allows to prevent γ% from the 10% drop out, then savings can be estimated by:

Savings=N× (CostSegBC-0.1×γ×CostDPOut)



Opposite are curve examples assuming that: 1) An automatic system cost $50 to segment, control, and report the index values; 2) retaining a single patient in the trial saves $80,000 and 3) γ can vary from 20% to 80%. These estimations are dramatically amplified with increasing dropout rate and related cost.

> “ The industry should embrace this novel biomarker and implement it in clinical trials”

Challenges with Widespread Adoption

In 2014 the Food and Drug Administration (FDA)[13] started to document the recourse of companion diagnostic along with the development of therapeutics. Eventually their co-development and the use of such companion diagnostic tools has been gaining traction[14]. This implies that when a drug is co-developed with a companion diagnostic biomarker, the drug in question is prescribed together with its companion tool in order to ensure the same outcomes achieved in clinical trials.

If imaging-based body composition assessments become a companion diagnostic for anti-cancer drugs, the companion imaging biomarker must be available without restriction and its use must be standardized using FDA approved software.

Therefore, the development of automated tools for tissue segmentation remains crucial for a more standardized and widespread adoption of this emerging biomarker.

Conclusions

Enabling the use of body composition indexes in oncology seems to be no more a matter of clinical evidence or lack of technology. Therefore, the industry should embrace this novel biomarker and implement it in clinical trials, to confirm the cost effectiveness ultimately improve clinical outcomes and patient care.

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