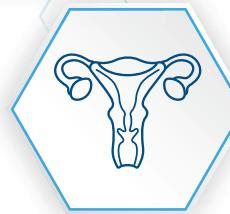
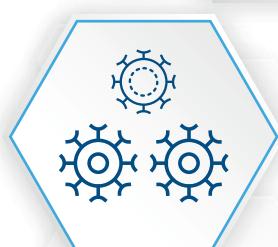
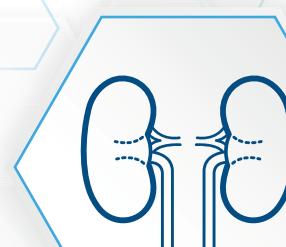


Gaining Clinically Relevant Insights in Obesity and Metabolic Diseases through Advanced Imaging Solutions



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Executive Summary

Obesity is now recognized as a chronic, systemic disease, with new clinical guidelines defining it based on specific signs of organ dysfunction and the distribution and amount of body fat.¹ The escalating global incidence rates of obesity represent one of the most serious public health challenges for societies and healthcare systems.

Without proper management, obesity shortens life and contributes to numerous chronic conditions, such as cardiovascular disease, diabetes, liver and kidney disease, as well as cancer.

In response to the dramatic increase in the prevalence and impact of obesity, the approach to its management has evolved rapidly:



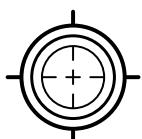
Beyond Weight Loss: The recent shift from focusing solely on weight loss as a clinical goal to addressing systemic effects of obesity marks a significant step in tackling this growing health crisis.



Advanced Therapies: The use of advanced therapies, such as incretins and next-generation anti-obesity medications, is essential for addressing the systemic and organ-specific complications of obesity and for providing more targeted treatments with reduced side effects.



Advanced Imaging: Advanced imaging technologies, particularly multi-organ MRI, are crucial for detailed assessments of organ health and body composition, helping to understand the full extent of organ dysfunction caused by obesity and the effects of therapeutic interventions. Perspectum, a global medical imaging platform company, operates on cloud-based Software as a Service model to integrate multi-organ MRI with AI-driven image analysis. This approach provides scalable solutions for clinical care and pharmaceutical research, empowering the development of targeted treatments to improve patient outcomes.



Enhanced Treatment Precision: Advanced imaging supports more precise patient selection and treatment customization, which are key to improving clinical outcomes.

Growing Demand for Effective Obesity Treatments and Multi-Organ Insights

Obesity is a complex chronic disease that significantly compromises quality of life and life expectancy, leading to early death and a myriad of chronic conditions. According to the World Obesity Federation, over 880 million adults were living with obesity in 2024,² and the global overweight and obesity prevalence is projected to reach 51% by 2035.³

The statistics concerning obesity-related comorbidities are even more alarming. For example, deaths from obesity-related cardiovascular disease have tripled over the last two decades.⁴ Similarly, mortality and disability linked to obesity-associated type 2 diabetes (T2D) have also increased more than threefold during the same period.⁵

Traditional weight loss strategies have prioritized reducing body weight, often neglecting the multifaceted impacts of obesity on various organs and tissues. However, recent advances in anti-obesity medications, particularly glucagon-like peptide-1 (GLP-1) receptor agonists and co-agonists are reshaping the clinical approach to obesity

It is essential we move beyond weight: organ health and body composition matter

management. For example, Eli Lilly's tirzepatide achieved an unprecedented level of 20.9% weight loss over 72 weeks in the SURMOUNT-1 trial.⁶ It also reduced the risk of heart failure outcomes by 38% in patients with heart failure with preserved ejection fraction (HFpEF) and obesity in the SUMMIT trial.⁷ Similarly, Novo Nordisk's semaglutide showed beneficial effects on patients with obesity HFpEF phenotype in the STEP-HFpEF clinical trial.⁸ In parallel, semaglutide demonstrated 24% reduction in the risk of kidney disease-related events in people with T2D and chronic kidney disease in the FLOW trial.⁹ These results demonstrate clinically meaningful improvements in organ function.



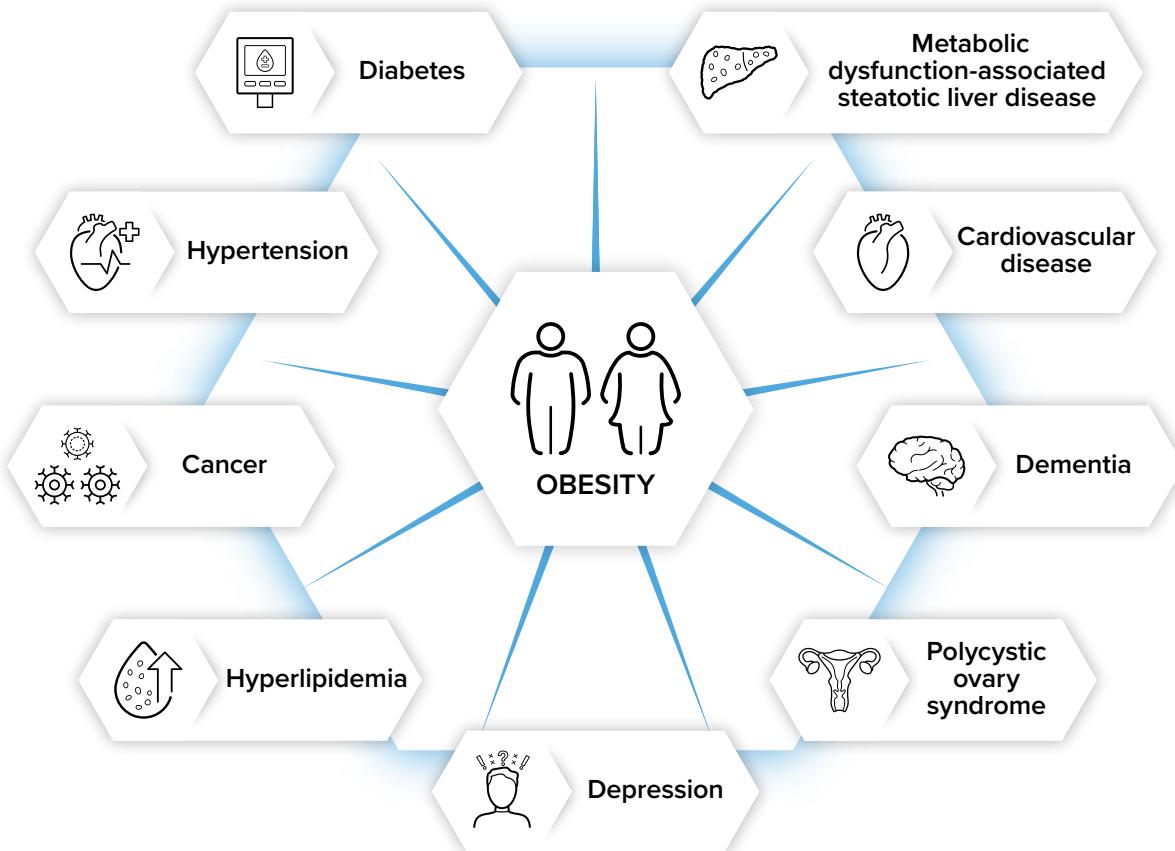
> 1 billion people

worldwide are now living with obesity²



51% by 2035

global overweight and obesity prevalence³



Another key indicator of the quality of weight loss is the relative loss of skeletal muscle versus fat mass, a subject of substantial recent attention.^{10,11} Skeletal muscle is increasingly being recognized as an independent marker of metabolic health. It is a key tissue in whole-body glucose homeostasis and a major site of lipid oxidation where it has a unique role in modulating whole-body fat balance via aerobic metabolism; it also significantly contributes to resting energy expenditure and hence energy demands.¹² A growing body of research demonstrates that decreased skeletal muscle mass and strength is associated with higher mortality risks of all causes, cardiovascular disease, cancer, and respiratory disease.¹³ Therefore, the goal of effective and safe weight loss interventions becomes not just targeting metabolically active adipose depots and improving organ health, but also minimizing the loss of muscle

mass. To date, the vast majority of studies on GLP-1 receptor agonists have relied on dual-energy X-ray absorptiometry (DXA) to evaluate body composition,¹¹ employing fat-free mass to measure all non-adipose tissue and serving as a crude surrogate measure of skeletal muscle. However, DXA does not directly measure skeletal muscle mass or assesses muscle quality (the amount of fat within the muscle and adverse muscle composition). Given the ongoing development of pharmacologic treatments designed to preserve muscle mass alongside GLP-1 therapies, there is a pressing need for more precise and comprehensive assessment methods. Advanced MRI techniques emerge as a superior alternative to DXA, providing both nuanced and comprehensive insights into body fat distribution, muscle quantity and quality, as well as liver, renal, and cardiac health.

Urgent Need for Advanced Imaging Tools in Obesity Research

Traditional methods for assessing body composition, such as BMI, waist circumference, waist-to-hip ratio, skinfold thickness, and bioelectrical impedance, each carry inherent limitations that can compromise their accuracy and clinical utility. While BMI is widely used, it fails to account for muscle mass, bone density, and subcutaneous and visceral fat, leading to potential misclassification across different ages, sexes, and ethnicities. Waist circumference and waist-to-hip ratio share similar limitations and are also prone to operator error and variability, while bioelectrical impedance analysis is influenced by factors such as hydration and physical activity, often requiring further validation against imaging techniques such as DXA or MRI.

Recognizing the shortcomings of BMI, a consortium of global experts has recently advocated for a paradigm shift in how obesity is defined and diagnosed. The new approach redefines obesity, moving beyond BMI as the sole indicator of obesity to a broader set of

criteria that recognize clinical obesity as a chronic, systemic disease characterized by alterations in the function of tissues, organs, the entire individual, or a combination thereof, due to excess adiposity.¹ The new diagnostic criteria emphasize the following:

*Excess adiposity should be confirmed by **direct measurement of body fat**, where available, and necessitate evidence of reduced **organ function** (...)¹*

These revised diagnostic criteria align closely with the recent FDA draft guidance which advises including imaging-based body composition measurements (e.g. by DXA or a suitable alternative such as MRI) to ensure a more accurate assessment of the quality of weight loss.¹⁴

DXA: A Limited Tool in Body Composition Analysis

Dual Energy X-Ray Absorptiometry (DXA or DEXA), initially developed for the assessment of bone mineral density, was subsequently upgraded to enable automatic derivation of overall adipose tissue and lean mass. By using two low-dose X-ray beams with differing energy levels, DXA differentiates tissue types based on their X-ray absorption rate, with denser tissues such as bone absorbing more energy.¹⁵ DXA is considered a reliable standard compared to traditional assessment methods, and it is characterized by rapid processing, low levels of ionizing radiation and relatively low cost. However, DXA has several limitations. Unlike CT and MRI, it cannot directly measure specific individual adipose tissue depots. The calibration of DXA machines utilizes standardized models that approximate the human body, but these models fall short in capturing individual variations, often resulting in estimates and potential inaccuracies rather than precise measurements. Another important challenge is that DXA can be influenced by hydration status and digestive tract content of patients, which can lead to overestimation of lean mass and underestimation of fat mass.¹⁶ In assessing weight loss quality, it is important to recognize that DXA does not directly measure

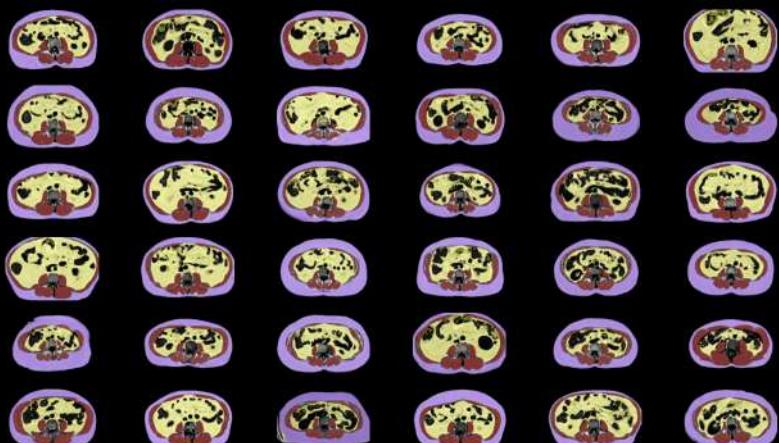
skeletal muscle mass; instead, it estimates fat-free mass (lean body mass and bone minerals) or lean tissue which includes both muscle and other non-fat tissues. Despite its limitations, most studies on GLP-1 receptor agonists have relied on DXA to evaluate body composition,¹¹ employing fat-free mass to measure all non-adipose tissue. Recent evidence has also revealed that DXA overestimates lean mass compared to MRI, the gold standard in this field. Specifically, DXA failed to detect a decrease of approximately 5% in muscle and lean mass,¹⁷ underscoring the need for future trials to consider MRI as the preferred method for detailed and accurate longitudinal assessment of body composition.

DXA does not provide direct measurements of fat depots or muscle mass. Future trials should prioritize MRI for detailed and accurate longitudinal assessments of body composition

MRI: Comprehensive Insights into Multi-Organ and Body Composition

Magnetic Resonance Imaging (MRI) is a non-invasive method, free of ionizing radiation, and widely recognized as the gold standard for body composition assessment. It utilizes strong magnetic fields (typically 1.5 Tesla or 3 Tesla) to align magnetic spins of protons within tissues. When exposed to a radio-frequency pulse, these protons absorb energy and shift alignment. As they return to their original alignment, they emit energy, which is detected by the MRI scanner to generate detailed images of the tissues. Unlike DXA, which relies on two-dimensional imaging and demographic data, MRI offers direct, three-dimensional assessments, providing precise volumetric measurements of organs, subcutaneous and visceral adipose tissue (VAT and SAT), ectopic organ fat, muscle volume and muscle fat infiltration. Recent validation studies have demonstrated that both single-slice and volumetric MRI body composition metrics maintain high technical performance across different scanner vendors and processing methods, with accuracy confirmed against manually segmented reference data¹⁹⁻²¹. This methodological flexibility facilitates reliable longitudinal monitoring and broader adoption across diverse research protocols and clinical workflows, accommodating varying resource constraints and study objectives. While computed tomography (CT) can, for example, differentiate between SAT and VAT, only MRI with its many sensitive and flexible contrast mechanisms, can quantify ectopic

fat. Moreover, as MRI does not use ionizing radiation, it is considered safer for repeated use in longitudinal studies and in children. MRI is the gold standard for the assessment of muscle volume and, unlike DXA, can also assess muscle fat infiltration. For example, a study examining muscle quality in 128 obese, non-diabetic women found that, compared to placebo, liraglutide reduced thigh muscle fat by 2.9% following 36 weeks of treatment. Additionally, it was observed that adverse muscle composition, characterized by high muscle fat and low muscle mass, was reduced compared to the placebo group.¹⁸ Understanding patterns of baseline muscle loss is essential in light of growing concerns over muscle preservation with new weight loss therapies. A large-scale population study examining natural weight loss patterns prior to the incretin era found that for every 5% drop in body weight, abdominal skeletal muscle volume accounted for 1.6% and muscle fat infiltration accounted for 2.3% of the total weight loss²². In addition, DXA measurements of lean mass correlated weakly with MRI-based skeletal muscle volume changes, underscoring the need for more comprehensive assessment methods. These findings, among many others, indicate that the reliance on limited measurement techniques, such as DXA, for assessing body composition after weight loss interventions may be inadequate for capturing the full scope of clinically relevant changes.



**SAME BMI
DIFFERENT
BODY
COMPOSITION...**

Apart from the measurements of adipose and muscle tissue, MRI enables a comprehensive assessment of abdominal organ health within a single scanning session, capturing clinically relevant changes such as hepatic steatosis, myocardial remodeling, renal hemodynamics and fibrosis. For example, MRI excels in advanced techniques such as proton density fat fraction (MRI-PDFF), a fast and reliable method for quantifying fat in tissues and organs. Using this approach enables precise, reproducible measurements of organ fat, which are crucial for diagnosing and monitoring other metabolic disorders, such as metabolic dysfunction-associated fatty liver disease (MASLD).

A recent large-scale study shows that MRI assessment of liver, heart, pancreas, and skeletal muscle can identify individuals

at highest risk of cardiometabolic complications²³. Critically, multi-organ MRI phenotyping can predict which patients with obesity will benefit most from specific treatments, with modelling estimates showing that targeted treatment selection could reduce the number needed to treat by ~8-fold for medications like tirzepatide²³. By shifting the focus from weight reduction to organ-specific outcomes and risk stratification, multi-organ MRI enables truly personalized treatment strategies that dramatically improve both clinical outcomes and cost-effectiveness, transforming obesity care from a one-size-fits-all approach to precision medicine.

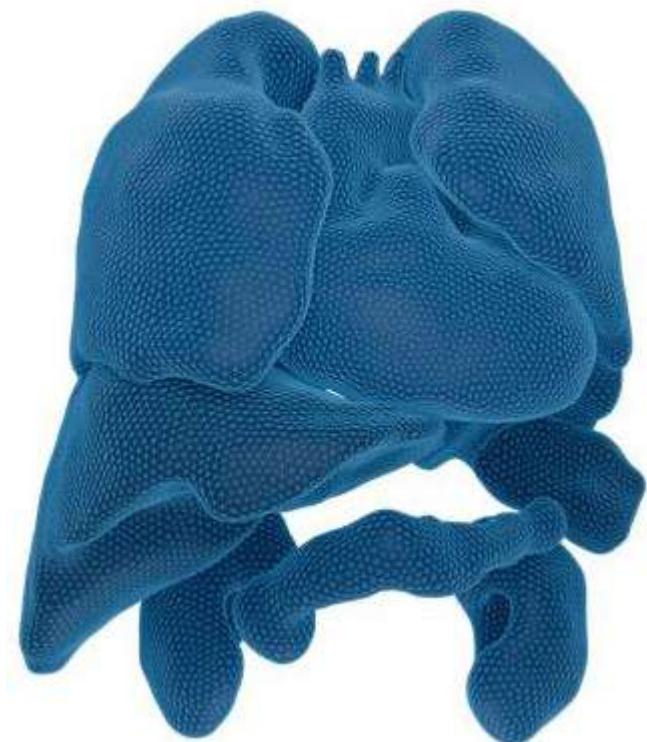


Perspectum's Role in Supporting Obesity and Metabolic Disease

Perspectum is a leading precision imaging provider, specializing in advanced MRI solutions for metabolic disease research and clinical care. With a portfolio of cutting-edge MRI tools, Perspectum provides holistic insights into fat distribution, organ function, and metabolic health. Having supported over 75 phase I to phase III commercial clinical trials, and with more than 150 peer-reviewed publications, Perspectum is a trusted partner in designing and executing imaging endpoints for clinical trials and research. We have extensive expertise in managing the complex operational environments associated with late phase trials, where our services cover protocol design, site selection and data management. By focusing on body composition as well as organ damage, Perspectum enables trial sponsors to uncover meaningful changes at scale, advancing obesity and metabolic disease management beyond traditional weight-based metrics assessments.

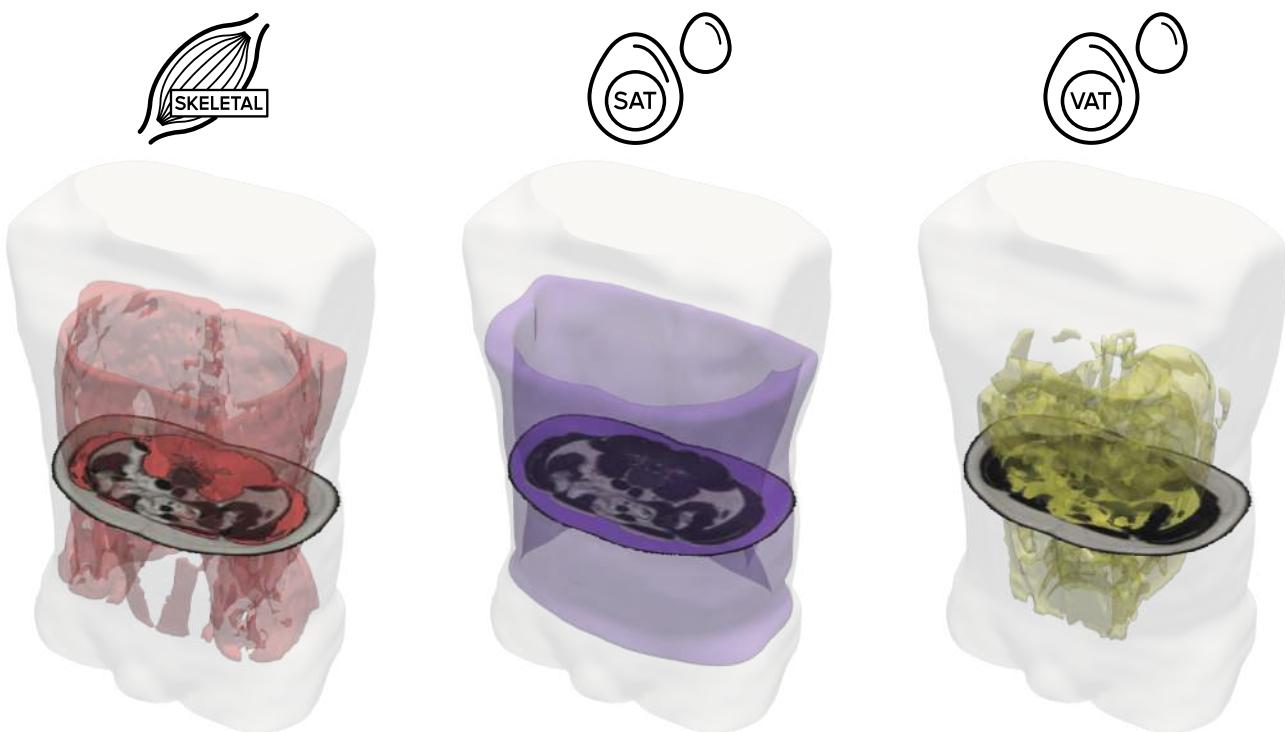
Perspectum's imaging solutions include DXA for body fat estimation and bone mineral density, along with advanced MRI techniques for precise body composition analysis. To enhance the efficiency and impact of obesity research, Perspectum delivers high-quality imaging data through optimized MRI protocols. Acquisition times are as short as 1 minute for single-slice (2D) assessments and 4-6

minutes for volumetric (3D) body composition evaluations. Metrics delivered include VAT, SAT, skeletal muscle and muscle fat infiltration, all of which are critical for understanding the scope of fat distribution in obesity and its complications in clinical trials. In addition to its role in research, Perspectum has expanded its imaging capabilities into clinical care with an FDA 510(k)-cleared medical device that provides accurate and precise, single-slice assessment of body composition at the L3 vertebra level.



Perspectum's imaging endpoints go beyond simple fat distribution by providing comprehensive multi-organ health insights across the liver, pancreas, heart, and kidneys. Given the established link between obesity and the development of heart failure with preserved ejection fraction (HFpEF), cardiac health assessments are essential in obesity management and in understanding the potential benefit of drugs in development for obesity. Perspectum's multi-organ MRI can capture both structural and functional cardiac data. Key metrics such as left ventricular ejection fraction (LVEF), left ventricular (LV) mass and LV increased filling pressure, left atrial (LA) volume and function, LV and LA strain, as well as T1 and T2 parametric mapping provide insights into the underlying pathophysiology, clinical profile and comorbidities of HFpEF. Additionally, the technology enables epicardial and pericardial fat assessments, critical biomarkers of cardiovascular risk.

Perspectum is at the forefront of metabolic dysfunction-associated steatohepatitis (MASH) research through its flagship product, LiverMultiScan – a multiparametric MRI tool that quantitatively characterizes liver tissue. LiverMultiScan delivers repeatable and reproducible biomarkers standardized across major scanner manufacturers (Siemens, GE, Philips, at 1.5T and 3T). The technology is FDA-cleared in the USA, CE-marked in the EU, and authorized in several Asia-Pacific (APAC) territories, with coverage from Medicare and commercial payers. LiverMultiScan has been deployed in over 50 interventional MASH trials, including Phase 3 studies, to identify eligible patients, enrich cohorts ahead of liver biopsy, and monitor therapeutic efficacy through early efficacy signals. The complex multi-organ and body composition in obesity underscores the need for integrated therapeutic approaches targeting multiple organ systems to mitigate the broad impact of metabolic dysfunction.



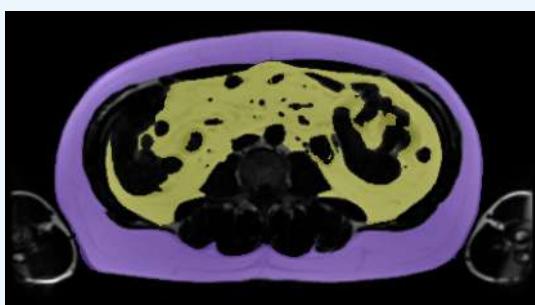
CASE STUDY 1

Beyond Weight: Adipose Tissue and Liver Health Improvements Despite <5% Change in Weight

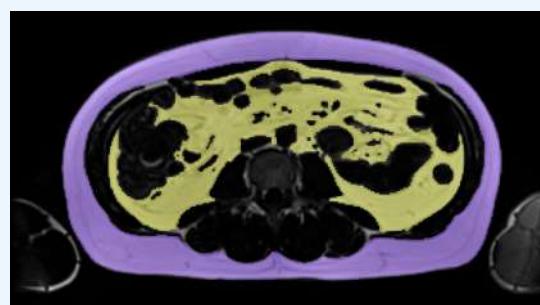
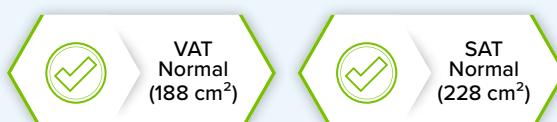
This case study involves a 42-year-old male with a 11-year history of type 2 diabetes, managed with metformin and GLP-1 receptor agonist. At the onset of the study, the patient weighed 99 kg. At 7-month follow-up, the patient's weight showed less than 5% change, yet pronounced improvements were observed in adipose tissue distribution and liver health, whereby his VAT and SAT decreased by 10% and 20%, respectively, and an 8% reduction in

liver fat content was observed. Additionally, there was a clinically significant reduction in liver disease activity, with his cT1 improving from 1050 ms to 948 ms (although still with at-risk MASH). This case underscores the limitations of weight as a sole indicator of metabolic health, highlighting the value of advanced imaging in capturing meaningful changes in fat distribution and liver health that are missed by traditional metrics.

BASELINE



FOLLOW-UP



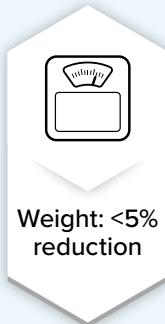
PRONOUNCED IMPROVEMENTS IN MRI METRICS

<5%

-10%

-20%

-8%

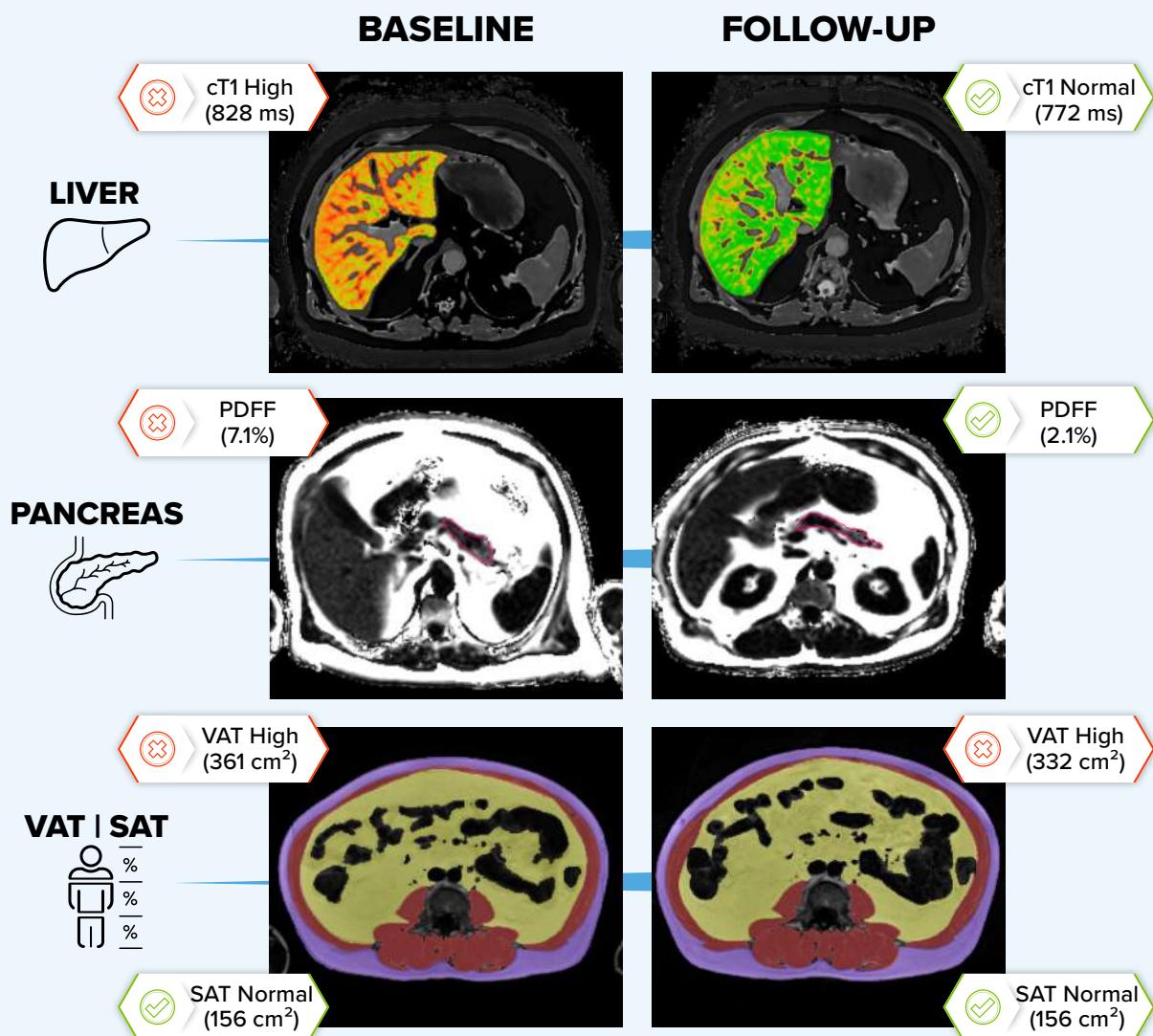


CASE STUDY 2

Beyond Fat: Multi-Organ Health Improvements

This case involves a 62-year-old male with a 12-year history of type 2 diabetes, BMI of 30 kg/m^2 , managed with metformin and sodium-glucose co-transporter-2 (SGLT2) inhibitors. At baseline, the patient weighed 83 kg, with elevated VAT and normal SAT. Over a 7-month period, despite no change in weight and persistently

high HbA1c (9.9%), advanced imaging revealed significant reductions in both pancreatic and liver fat. VAT remained elevated and SAT normal at follow-up, similarly to baseline. This case highlights the importance of evaluating multi-organ outcomes in obesity management.



Expertise in Project Management and Collaborative Opportunities

At Perspectum, we go beyond advanced imaging by providing comprehensive site and project management services to support the successful execution of multi-center trials. Our approach integrates standardized protocols, scalability, and deep biomarker expertise, delivering precise, actionable insights for clinical research.

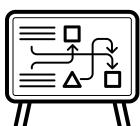
Perspectum's Standardization Program



Consistency Across Sites: In line with the Clinical Trial Imaging Endpoint Process Standards Guidance for Industry, Perspectum aids in standardization across large, multi-center studies through the provision of trial-specific imaging manuals (imaging acquisition protocol), outlining subject positioning, anatomical coverage of the scan, and scanner settings and sequences required for correct image acquisition prior to site activation.



Quality Assurance: The process includes phantom scans to verify scanner calibration and a standardized process for image verification, pre-processing, and quantification to ensure technical accuracy. Additionally, central reads are performed by in-house MRI analysts using standardized reporting templates to minimize variability and ensure consistent high-quality datasets.



Guidance and Protocol Design: Perspectum offers expert advice to tailor imaging protocols for optimal trial outcomes, leveraging extensive biomarker expertise.

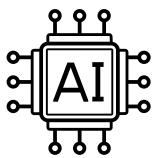
Deep Biomarker Expertise



Innovative Health Solutions: Perspectum focuses on scalable health solutions driven by advanced physics and artificial intelligence (AI), developing algorithms informed by data from research collaborations. We use **deep learning algorithms** that achieve **human-level performance** with far fewer data samples than traditional methods, making our tools more efficient and scalable.



Comprehensive Data Analysis: Our technology allows for **rapid analysis** of complex health data from both individual patients and large cohorts, enabling meaningful comparisons between healthy and diseased populations and facilitating outcome predictions for individuals. By analyzing large databases, such as the UK Biobank, we can identify population health patterns that inform product development and continuous improvement.



AI-Driven Imaging: The key component of Perspectum's expertise in MRI is the integration of MRI physics with downstream image analysis. Our AI comprises a mix of traditional computer vision, statistical techniques, and deep convolutional neural networks, integrated into regulatory-cleared medical devices (FDA-cleared and CE-marked).



IP Portfolio: Perspectum's strong IP portfolio covers imaging technologies for the liver, kidneys, pancreas, and overall body composition. Our translational sciences capabilities apply this expertise to a range of diseases, including obesity, metabolic dysfunction-associated steatohepatitis, type 2 diabetes, heart failure, chronic kidney disease, and cancer.

Scalability

Global Network: Access to our extensive and ever-expanding global network of over **750 imaging centers** facilitates rapid trial start-up and scalability. Furthermore, strategic partnerships such as our collaboration with Microsoft Nuance allow us to deliver our integrated digital platform suite for metabolic disease at scale. This commitment to scalability is supported by recent estimates that there are as many as 50,000 MRI scanners installed globally. As many of the fat mapping and multi-organ imaging techniques described herein do not require additional scanner hardware or software upgrades, this suggests that an adequate number of scanners exists to support the use of MRI endpoints across a multitude of large, multi-center studies.

Though the initial costs associated with including MRI in obesity and metabolic disease clinical trials may be higher than opting for traditional endpoints, these costs are offset by enhancements in trial efficiency. The use of MRI endpoints offers improved precision compared to other techniques, allowing for reductions in sample size and trial duration, lowering overall costs. Similarly, reducing the reliance on invasive procedures, such as liver biopsy in the case of MASLD/MASH trials, helps reduce both burden and risk to study participants, enhancing recruitment and retention rates. These advantages collectively position the use of MRI as a cost-effective choice in obesity and metabolic disease clinical trials.

The use of MRI endpoints offers improved precision compared to other techniques, allowing for reductions in sample size and trial duration, lowering overall costs.

Integration with large, full service CROs

Perspectum provides seamless integration with main contract research organizations (CROs), enhancing patient stratification, endpoint reliability and data reproducibility. These collaborations enable efficient trial workflows by combining imaging innovation

with logistical and regulatory expertise of larger CROs, accelerating timelines and improving the quality of clinical outcomes leading to greater precision in trial design and execution – especially in complex therapeutic areas such as metabolic diseases.

Data Management Capabilities

Perspectum operates an ISO 27001-certified, 21 CFR Part 11-, GDPR-, and HIPAA compliant trial management system for data capture, patient tracking, and imaging data management. The Perspectum Portal is a cloud-based data management platform that facilitates secure data upload, customizable user permissions, and daily notifications to sites and sponsors. The portal is routinely used for the receipt

and the storage of raw imaging data and results. Perspectum operates on a Software as a Service model, with infrastructure and workflows that have great scalability for a breadth of imaging modalities, including MRI, DXA, ultrasound, digital pathology, and endoscopy, ensuring scalability for Phase 3 trials.

Towards Action: Conclusion and Recommendations

The increasing prevalence of obesity and its associated metabolic diseases highlights the critical need for more precise and targeted interventions. Traditional metrics like BMI and body weight fall short in capturing the full impact of obesity on multi-organ health. Advanced imaging modalities, particularly multi-organ MRI, offer a more comprehensive understanding of obesity and related comorbidities, improving patient stratification and therapeutic monitoring. Additionally, the accuracy and reproducibility of multi-organ MRI provides an opportunity for improved fidelity of data in longitudinal studies, enabling more reliable tracking of disease progression and treatment effects.

As we confront the challenges of the obesity epidemic, it is imperative to adopt these innovative approaches within clinical research and practice. Collaboration between leaders in the field will be key to advancing obesity research and developing more effective therapies. To explore how these innovations can benefit your research, visit www.perspectum.com



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