DOI: 10.19271/IRONS-000150-2021-37

#### **REVIEW ARTICLE**

# ARTIFICIAL INTELLIGENCE FOR EARLY DETECTION AND MANAGEMENT OF MUSCULOSKELETAL COMPLICATIONS POST HEMATOPOIETIC CELL TRANSPLANT. FUTURE PERSPECTIVES

SZTUCZNA INTELIGENCJA DO WCZESNEGO WYKRYWANIA I ZARZĄDZANIA POWIKŁANIAMI UKŁADU MIĘŚNIOWO-SZKIELETOWEGO PO PRZESZCZEPIENIU KOMÓREK KRWIOTWÓRCZYCH. PERSPEKTYWY NA PRZYSZŁOŚĆ

# Jaleel Mohammed<sup>1</sup>, Jayanti Rai<sup>2</sup>, Hadeel Bakhsh<sup>3</sup>, Julie Hobbs<sup>4</sup>, Shahrukh Hashmi<sup>5</sup>

- <sup>1</sup>Lincolnshire Community Health Services NHS Trust, UK
- <sup>2</sup>Kent Community Health NHS Foundation Trust, UK; Scientific Committee Chair, The European Society for Shoulder and Elbow Rehabilitation, Geneva, Switzerland
- <sup>3</sup>Princess Nourah Bint Abdulrahman Universiy, Riyadh, Saudi Arabia
- <sup>4</sup>International Operations, Mayo Clinic, Rochester, USA
- <sup>5</sup>Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA

## **ABSTRACT**

#### Introduction

To help monitor and manage complications, monitor disease progression, and help lower morbidity and mortality rates in Hematopoietic cell transplant (HCT) patients, the use of artificial intelligence technology can prove to be an efficient tool.

## Aim

We propose a futuristic vision of an artificial intelligence model which could help in early detection of MSK related complications, improve communication between HCT healthcare professional team, improve diagnostics via machine learning (ML), help monitor symptom/disease progression remotely, and help integrate services for a more patient-friendly service delivery, i.e., drug prescription, exercise prescription, appointment tracking, referral pathways.

# Materials and methods

The proposed model is a three-phase integrated program where musculoskeletal physical examination is combined with wearable textiles interface platform and machine learning algorithms, thereby providing live and remote feedback of changes as they happen in at the musculoskeletal and vital signs level.

# Result

With the help of machine learning technology, various algorithms can be created to help improve remote and live diagnostic accuracy of post-HCT musculoskeletal manifestations. Subtle changes over the course of time in various patient groups can be detected at the skin, fascia, muscle, bone level; thereby helping in better understanding of the disease and its management.

## **Conclusion**

A futuristic machine-learning artificial intelligence program combined with wearable devices and the expertise of the clinicians can significantly change the way healthcare professionals and patients manage post-HCT complications and the resultant being improved quality of life in survivors of HCT.

**Keywords:** hematopoietic cell transplant, rehabilitation, artificial intelligence, physiotherapy, occupational therapy.

# **STRESZCZENIE**

# Wstęp

Aby pomóc w monitorowaniu i zarządzaniu powikłaniami, monitorowaniu postępu choroby oraz obniżaniu zachorowalności i śmiertelności u pacjentów po przeszczepieniu komórek krwiotwórczych (HCT), zastosowanie technologii sztucznej inteligencji może okazać się skutecznym narzędziem.

## Cel

Zostanie zaproponowana przyszłościowa wizja modelu sztucznej inteligencji, która może pomóc we wczesnym wykrywaniu powikłań związanych z układem mięśniowo-szkieletowym, poprawić komunikację między zespołem pracowników służby zdrowia HCT, poprawić diagnostykę poprzez uczenie maszynowe (ML), pomóc zdalnie monitorować postęp objawów choroby i pomóc zintegrować usługi w celu świadczenia usług bardziej przyjaznych dla pacjenta, tj. przepisywanie leków, zaleceń ćwiczeń, śledzenie wizyt, ścieżki skierowań.

## Materialy i metody

Proponowany model jest trójfazowym zintegrowanym programem, w którym badanie fizykalne układu mięśniowo-szkieletowego jest połączone z platformą interfejsu w noszonych tekstyliach i algorytmami uczenia maszynowego, zapewniając w ten sposób dopływ bieżących i zdalnych informacji zwrotnych o zmianach zachodzących na poziomie układu mięśniowo-szkieletowego i funkcji życiowych.

## Wyniki

Za pomocą technologii uczenia maszynowego można stworzyć różne algorytmy, które pomogą poprawić zdalną i rzeczywistą dokładność diagnostyczną objawów chorób mięśniowoszkieletowych po HCT. Subtelne zmiany z biegiem czasu w różnych grupach pacjentów można wykryć na poziomie skóry, powięzi, mięśni i kości; w ten sposób pomagając w lepszym zrozumieniu choroby i jej leczenia.

# Wnioski

Przyszłościowy program sztucznej inteligencji wykorzystujący uczenie maszynowe w połączeniu z urządzeniami do noszenia i specjalistyczną wiedzą klinicystów może znacząco zmienić sposób, w jaki pracownicy służby zdrowia i pacjenci radzą sobie z powikłaniami po HCT, czego rezultatem jest poprawa jakości życia osób, które przeżyły HCT.

**Słowa kluczowe:** przeszczep komórek krwiotwórczych, rehabilitacja, sztuczna inteligencja, fizjoterapia, terapia zajęciowa.

## Introduction

Haematopoietic cell transplant (HCT) patients require long-term follow-up and monitoring to help manage transplant-related complications, check disease progression, and to help lower morbidity and mortality rates (Hierlmeier *et al.*, 2018). Although the overall survival rate among HCT patients is improving, the costs associated with survivorshiprelated complications are on the rise too (Brice *et al.*, 2017; Svahn *et al.*, 2012).

The MSK (musculoskeletal) post-HCT complications can be disease-induced, treatment-induced, or drug-induced and can affect various organs and structures in the body resulting in complications such as avascular necrosis of the bones, steroid-induced myopathy, fatigue, fasciitis, scleroderma, neuropathy, joint destruction, osteoporosis and reduced lung capacity (Smith et al., 2015; Haruki et al., 2012; Ishikawa et al., 2019). Furthermore, the impact and extent of MSK involvement also vary from patient to patient, with some developing complications to one or two limbs while others can suffer from multiple site involvement.

In ideal care settings, regular screening should be an integral part of the post-HCT care package, but anecdotal evidence suggests that this is often missed due to various reasons, including lack of knowledge in patients about early reporting, knowing what is normal to abnormal presentation, and clinicians lack of time and resources. Furthermore, even when the post-HCT complication has been identified, patients have also reported delay in getting timely care which has been attributed to lack of communication between healthcare specialities, the number of different appointments a patient has to keep track of during the treatment cycle, travel distance to various speciality, cross-referral to other specialities and the duration it takes to set an appointment, and lack of exchange of patient care plan between healthcare professionals (Mehaan et al., 2005; Booker et al., 2016; Shah et al., 2018).

# Aim

We propose a futuristic vision where the integration of artificial intelligence (AI) and machine learning (ML) can help clinicians and patients in the early identification and management of treatment-related musculoskeletal complications post HCT. Furthermore, the proposed AI and ML model can also help improve communication between various specialities involved in patient care, help automate the referral process, thereby reducing delay in patient care.

# Material and methods

Current diagnostic technology for HCT-related musculoskeletal manifestations

The diagnosis of a majority of MSK manifestations, although it can involve various tests and scans, the diagnostic ultrasound scan (US) is becoming the most widely used and popular diagnostic tool (Zaidman and Van Alfen 2016; Ortiz et al., 2021). With improved technology, US imaging has quickly gained its popularity and is currently the most widely used diagnostic tool for MSK diseases for its accuracy, reliability, and in some cases, eliminating the need for expensive investigations like magnetic resonance imaging (MRI) (Henderson et al., 2015; He et al., 2018). MSK US scan is currently used in various settings and includes measurement of facial thickness/ dermal thickness, muscle size (myopathy) and bone quality, osteoporosis, and osteopenia for early detection and prevention (Lee et al., 2017; Nijholt et al., 2017). Ultrasound imaging has also been found to be a quantitative, cost-effective, valid, reliable, non-invasive, diagnostic, and prognostic tool for not only measuring the plantar fascia thickness but also for identifying abnormal thickening (Huerta and García 2007; Abdelaal et al., 2020).

Proposed AI model for identifying HCT MSK manifestations

The promise of artificial intelligence (AI) in health care offers substantial opportunities to improve patient care, clinical outcomes, reduce costs, and over-service delivery. The use of AI in physiotherapy (PT) and occupational therapy (OT) has significantly evolved in the past two decades. Its use has primarily been seen in rehabilitation settings like stroke, Parkinson's, and cardiac rehabilitation, and in some instances, claims of AI exceeding the conventional rehabilitation approaches (Jovanov *et al.*, 2005; Pazzaglia *et al.*, 2020; Hung *et al.*, 2017). However, there has been very minimal focus on ML and AI for the diagnostic US in the MSK context.

#### Result

The ML and AI model for early detection of HCT-MSK manifestations has been described in three phases below, and Fig. 1 illustrates the phases.

## Phase I

During phase I, each patient will undergo an extensive physical assessment which will include a joint range of motion assessment for upper and lower extremities, skin thickness, gait analysis, heart rate, and bone scan. Each patient can be provided with the wearables during their discharge from the hospital, a customised fabric clothing combining capacitive micromachined ultrasound transducers (CMUTs) and wearable sensors, or inertial measurement units containing accelerometers and gyroscopes, with or without a magnetometer to help capture both the skin/ fascia thickness and the joint range of motion (Gerardo et al., 2020; Walmsley et al., 2018). Furthermore, wearable inertial sensors can also be embedded into the fabric design to help with range of motion, gait analysis, early identification of gait and balance disturbances, muscle force, and recommend timely intervention, and monitor progress in realtime (Camomilla et al., 2018). Lastly, these smart clothes can also be integrated to read and transmit ECG signals for safe exercise monitoring (Sundaram et al., 2019).

The wearables will include a full sleeves t-shirt, undergarments (male/female), socks, and gloves, all custom designed for carrying

out real-time scanning, recording movements in the upper and lower limb, and gait analysis. A secure mobile-friendly app and web-based application will also be made available to the patient, which will provide them with outcome measures in a simplified fashion and also the option of reporting any symptoms to the healthcare team via the application. The web-based application will also provide a platform for a two-way interaction between the patient and the authorised healthcare professionals involved in patient care. The platform will also be integrated to provide patients with information on their medications, appointments, exercise program, exercise adherence, day-to-day SpO2, and Hb levels for safe activity.

# Phase II

During phase II, the integrated wearables will provide extensive data to the AI system to enable supervised ML, which will be used for training data and evolving algorithms for classification and for developing unsupervised ML for diagnosis and progress monitoring.

Day-to-day readings on patients' skin thickness measurement, active range of motion scores, gait analysis, SpO2, and Hb will be remotely sent to the secure central data storage for analysis. Any changes in the reading will be compared to the initial physical assessment scores will be highlighted, and the decision will be made by the healthcare team if any intervention is needed.

## Phase III

In Phase III, the patient will be provided timely feedback, intervention, appointments, and a treatment plan to reflect necessary changes observed from the data. This phase is also where the AI will provide all the data to help supervised ML develop into nonsupervised ML for the automation of the process.

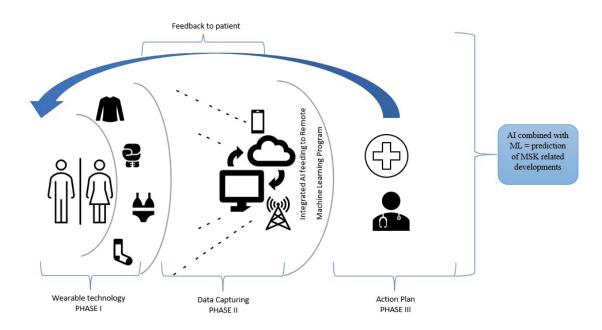
Once a sufficient amount of data has been entered into the ML, the futuristic AI model will allow a non-supervised learnt ML to make automated decisions as per the pre-set

algorithms for patients using the web-based or app-based platform as follows:

- a) Flag any changes in the readings to the concerned healthcare professional.
- b) Communicate the scores to the patient and initiate referrals as appropriate to PT, OT, orthopaedics, transplant physicians, dermatology, and other specialities.
- c) Prescribe individualised exercise program to the patient as per the MSK changes.
- d) Make individualised recommendation for patients on activity and progression as per their daily SpO2 and Hb.

which restricts their participation in activities of daily living and social participation (Colman *et al.*, 2020). For the readers, we have provided a select few details of some of the MSK manifestation in this patient group below:

Skin & Fascia – Scleroderma causes the skin to become thick and tight, limiting joint function and, in some cases, affecting internal organs of the body. Some patients may present with deep tissue sclerosis with or without the manifestation of superficial sclerosis, which can make early diagnosis even more challenging. The Modified Rodnan total skin thickness



 $\textbf{Figure 1.} \ \textbf{Illustration of AI and ML integration solution for post-HCT MSK manifestation}.$ 

## Discussion

The most common MSK related complications affecting patients' quality of life from an MSK rehabilitation perspective are poor muscle strength that results in functional incapacity in activities of daily living (ADL), tightness of skin and fascia leading to contractures, and bone complications associated with osteoporosis, necrosis, and fractures, resulting in joint destruction capacity (Smith *et al.*, 2015; Haruki *et al.*, 2012; Ishikawa *et al.*, 2019). Consequently, patients are at an increased risk of experiencing performance limitations

score (mRSS) for scleroderma and subjective measures such as clinical presentation and site palpation for thickness in the fascia are largely used for diagnosis.

Muscle – Myositis is one of the common clinical presentations in HCT patients, which results in proximal muscle weakness and myalgia. Some patients also develop further complications, including degeneration, necrosis, and infiltration of inflammatory cells. Bone – Generalised osteopenia, poor bone health, osteoporosis, avascular necrosis,

and fractures related to bone fragility are

some of the common problems faced by the patient with Graft Versus Host Disease (GVHD). Symptoms experienced by the patients typically include pain, joint swelling, difficulty in performing daily life activities, increased pain in weight-bearing joints, and poor functional performance.

With the advancements in the ML technology and AI logarithms, MSK clinicians can remotely monitor and report tissue or bone level changes in patients as they develop (Sethi et al., 2020). Wearable technology makes it easy not only to record outcome measures remotely but combining this with the Internet of Everything (IoE) and "Energy for the New Era" makes it possible for the machine to learn, interpret results and deliver response, trigger treatment protocols, create automatic appointments for patients to benefit from timely intervention, monitor tissue-level changes as they happen (Miraz et al., 2015; Adams et al., 2019).

An interface platform using wearable textiles, also known as smart textiles or e-textiles, are adaptable, flexible to allow human motion, comfortable to wear, and can be easily integrated with machine technology can be used to design bespoke clothing which can directly relay live feed to remote monitors (Kos and Umek 2018; Zeng et al., 2014; Cherenack and Van Pieterson 2012).

# AI and Safety Concerns

Despite the widespread use of intelligent applications in healthcare, there remain challenges to their adoption and full integration. Like any other technology, AI can pose various risks ranging from software failure, data compromise, recording and creating algorithms, patient safety, and errors in the application of knowledge to the patient population (Macrae 2019). Furthermore, there is also the issue of trust at both the patient and healthcare professional end with regards to the usage and safety of AI (Nundy et al., 2019). However, for the past few decades, this rapidly growing industry has been continually investing time, energy, and resources in developing safer

and more secure technology by introducing various measures like improved cybersecurity, safer AI and MI designs, procedural safeguards, and more robust education for patients and healthcare professionals on the use of such technology (Ellahham *et al.*, 2020).

# **Conclusions**

A futuristic ML and AL program combined with wearable devices and the clinical expertise of the healthcare professionals can significantly change the way we manage post-HCT MSK complications. We envisage that the proposed model can not only help in the early detection of complications but can also help in early intervention, better patient-clinician communication, and improved survivorship in HCT patients. There is an urgent need for high-quality clinical trials involving innovative futuristic technology aimed at early diagnosis and management of HCT related complications.

#### REFERENCES

Abdelaal, E., Khater, M., Gobran, H. and Esmail, H. (2020) 'Role of Ultrasonography and Magnetic Resonance Imaging in Assessment of Plantar Fasciitis'. Zagazig University Medical Journal, 26(6), pp. 1030–1037.

Adams, R.J., Ellington, A.L., Armstead, K., Sheffield, K., Patrie, J.T., and Diamond, P.T., (2019) 'Upper extremity function assessment using a glove orthosis and virtual reality system'. OTJR: occupation, participation, and health, 39(2), pp. 81–89.

Booker, R., Simon, J., Raffin Bouchal, S. and Advanced Care Planning CRIO Program, (2016) 'Patient, family member, and clinician perspectives on advance care planning (ACP) in hematology and hematopoietic stem cell transplantation' (HSCT).

Brice, L., Gilroy, N., Dyer, G., Kabir, M., Greenwood, M., Larsen, S., Moore, J., Kwan, J., Hertzberg, M., Brown, L. and Hogg, M., (2017). 'Haematopoietic stem cell transplantation survivorship and quality of life: is it a small world after all?'. Supportive Care in Cancer, 25(2), pp. 421–427.

Camomilla, V., Bergamini, E., Fantozzi, S. and Vannozzi, G., (2018) 'Trends supporting the in-field use of wearable inertial sensors for sport performance evaluation: A systematic review'. Sensors, 18(3), p. 873.

Cherenack, K. and Van Pieterson, L., (2012) 'Smart textiles: Challenges and opportunities'. Journal of Applied Physics, 112(9), p. 091301. Colman, J., Casto, S.C., Wisner, E., Stanek, J.R. and Auletta, J.J., (2020) 'Improving Occupational Performance in Pediatric Hematopoietic Cell Transplant Recipients'. American Journal of Occupational Therapy, 74(5), pp. 7405205020p1–7405205020p11.

**Ellahham, S., Ellahham, N. and Simsekler, M.C.E.,** (2020) 'Application of artificial intelligence in the health care safety context: opportunities and challenges'. American Journal of Medical Quality, 35(4), pp. 341–348.

Gerardo, C.D., Cretu, E. and Rohling, R., (2018) 'Fabrication and testing of polymer-based capacitive micromachined ultrasound transducers for medical imaging'. Microsystems & nanoengineering, 4(1), pp. 1–12.

Haruki, H., Koga, M., Ogasawara, J.I., Omoto, M., Kawai, M. and Kanda, T., (2012) 'Neuropathy in chronic graft-versus-host disease caused by Donor T cells'. Muscle & nerve, 46(4), pp. 610–611.

He, L., Delzell, P. and Schils, J., (2018) 'Comparison of MRI findings after musculoskeletal ultrasound: an opportunity to reduce redundant imaging'. Journal of the American College of Radiology, 15(8), pp. 1116–1119. Henderson, R.E., Walker, B.F. and Young, K.J., (2015) 'The accuracy of diagnostic ultrasound imaging for musculoskeletal soft tissue pathology of the extremities: a comprehensive review of the literature'. Chiropractic & manual therapies, 23(1), pp. 1–29.

Hierlmeier, S., Eyrich, M., Wölfl, M., Schlegel, P.G. and Wiegering, V., (2018) 'Early and late complications following hematopoietic stem cell transplantation in pediatric patients—A retrospective analysis over 11 years'. PloS one, 13(10), p. e0204914.

**Huerta, J.P. and García, J.M.A.,** (2007) 'Effect of gender, age and anthropometric variables

on plantar fascia thickness at different locations in asymptomatic subjects'. European journal of radiology, 62(3), pp. 449–453.

Hung, Y.H., Chen, P.J. and Lin, W.Z., (2017) 'Design factors and opportunities of rehabilitation robots in upper-limb training after stroke'. In 2017 14th International Conference on Ubiquitous Robots and Ambient Intelligence (URAI) (pp. 650–654). IEEE.

Ishikawa, A., Otaka, Y., Kamisako, M., Suzuki, T., Miyata, C., Tsuji, T., Matsumoto, H., Kato, J., Mori, T., Okamoto, S. and Liu, M., (2019) 'Factors affecting lower limb muscle strength and cardiopulmonary fitness after allogeneic hematopoietic stem cell transplantation'. Supportive Care in Cancer, 27(5), pp. 1793–1800. Jovanov, E., Milenkovic, A., Otto, C. and De Groen, P.C., (2005) 'A wireless body area network of intelligent motion sensors for computer assisted physical rehabilitation'. Journal of NeuroEngineering and rehabilitation, 2(1), pp. 1–10.

**Kos, A. and Umek, A.,** (2018) 'Wearable sensor devices for prevention and rehabilitation in healthcare: Swimming exercise with real-time therapist feedback'. IEEE internet of things journal, 6(2), pp. 1331–1341.

**Macrae, C.,** (2019) 'Governing the safety of artificial intelligence in healthcare'. BMJ quality & safety, 28(6), pp. 495–498.

Medsger Jr, T.A. and Benedek, T.G., (2019) 'History of skin thickness assessment and the Rodnan skin thickness scoring method in systemic sclerosis'. Journal of Scleroderma and Related Disorders, 4(2), pp. 83–88.

Meehan, K.R., Root, L., Kimtis, E.A., Patchett, L. and Hill, J.M., (2005) 'Shared medical appointments (SMA): Implementation in the bone marrow transplantation clinic'. Biology of Blood and Marrow Transplantation, 11(2), pp. 93–94.

Meehan, K.R., Root, L., Kimtis, E.A., Patchett, L. and Hill, J.M., (2005) 'Shared medical appointments (SMA): Implementation in the bone marrow transplantation clinic'. Biology of Blood and Marrow Transplantation, 11(2), pp. 93–94.

Miraz, M.H., Ali, M., Excell, P.S. and Picking, R., (2015) 'September. A review on Internet of Things (IoT), Internet of everything (IoE) and Internet of nano things (IoNT)'. In 2015 Internet Technologies and Applications (ITA) pp. 219–224. IEEE.

Nijholt, W., Scafoglieri, A., Jager-Wittenaar, H., Hobbelen, J.S. and van der Schans, C.P., (2017) 'The reliability and validity of ultrasound to quantify muscles in older adults: a systematic review'. Journal of cachexia, sarcopenia and muscle, 8(5), pp. 702–712. Nundy, S., Montgomery, T. and Wachter, R.M., (2019) 'Promoting trust between patients and physicians in the era of artificial intelligence'. Jama, 322(6), pp. 497–498.

Ortiz, A.F.H., Guevara, S.Z., Ramírez, S.M., Rojas, J.C., Malo, R.G., Beaujon, L.F., Ochoa, M.M., Zarate, J.F., Niño, M.F. and Aguilar, M.O., (2021) 'What is the role of ultrasonography in the early diagnosis of scaphoid fractures?'. European Journal of Radiology Open, 8, p. 100358.

Pazzaglia, C., Imbimbo, I., Tranchita, E., Minganti, C., Ricciardi, D., Monaco, R.L., Parisi, A. and Padua, L., (2020) 'Comparison of virtual reality rehabilitation and conventional rehabilitation in Parkinson's disease: A randomised controlled trial'. Physiotherapy, 106, pp. 36–42. Sethi, A., Ting, J., Allen, M., Clark, W. and Weber, D., (2020) 'Advances in motion and electromyography based wearable technology for upper extremity function rehabilitation: A review'. Journal of Hand Therapy, 33(2), pp. 180–187.

Shah, G.L., Majhail, N., Khera, N. and Giralt, S., (2018) 'Value-based care in hematopoietic cell transplantation and cellular therapy: challenges and opportunities'. Current hematologic malignancy reports, 13(2), pp. 125–134. Smith, S.R., Haig, A.J. and Couriel, D.R., (2015) 'Musculoskeletal, neurologic, and cardiopulmonary aspects of physical rehabilitation in patients with chronic graft-versus-host disease'. Biology of Blood and Marrow Transplantation, 21(5), pp. 799–808.

**Sundaram, P.S.S., Basker, N.H. and Natrayan, L.,** (2019) 'Smart clothes with bio-sensors

for ECG monitoring. International Journal of Innovative Technology and Exploring Engineering, 8(4), pp. 298–30.

Svahn, B.M., Remberger, M., Alvin, O., Karlsson, H. and Ringden, O., (2012) 'Increased costs after allogeneic haematopoietic SCT are associated with major complications and re-transplantation'. Bone marrow transplantation, 47(5), pp. 706–715.

Walmsley, C.P., Williams, S.A., Grisbrook, T., Elliott, C., Imms, C. and Campbell, A., (2018) 'Measurement of upper limb range of motion using wearable sensors: a systematic review'. Sports medicine-open, 4(1), pp. 1–22.

**Zaidman, C.M. and Van Alfen, N.,** (2016) 'Ultrasound in the assessment of myopathic disorders'. Journal of Clinical Neurophysiology, 33(2), pp. 103–111.

Zeng, W., Shu, L., Li, Q., Chen, S., Wang, F. and Tao, X.M., (2014) 'Fiber-based wearable electronics: a review of materials, fabrication, devices, and applications'. Advanced materials, 26(31), pp. 5310–5336.