This report is comprised of relevant and updated findings available. In accordance with the provided personal details, and pre-defined questions we have indicated data and insights taken from various sources of information. These insights aim to inform and enhance future decisions. In no circumstances the information contained in this report or any information given in the process are intended or implied to be a substitute for professional medical advice. It is provided for informative purposes only. We have given careful thought in order to construct the report in a way that suits both patients and physicians. We strongly encourage you to use this report and consult your physician before making any medical decisions.

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Methodology

This is a personal health meta-research designed to address specific pre-defined queries. For that purpose, we have conducted an extensive search through relevant medical databases, journals, and other trusted sources. We have also reviewed unofficial platforms such as relevant social media, forums and blogs and extracted insights from similar patients relevant as much as these were relevant to the situation at hand. We have analyzed the data, evaluated the reliability of the sources of information and the relevancy to the specific case. Finally, we have assembled all insights into an actionable report, which has been reviewed by a senior analyst.

Health reports tend to be complicated to read, so in order to ease the process for the patient we have highlighted parts, which we found important. We also added references as endnotes for sources of information that the patient or his/her physician wishes to further explore. Additional information such as patient's testimonials is added in the footnotes.

This report contains:

1. Meta-Research
2. Report Summary
3. Doctor's Letter

Diagnosis Summary

A 1.9-years-old male patient was diagnosed with Mucopolysaccharidoses (MPS) 2 (Hunter syndrome) in April 2019, after a history of recurrent fevers, splenomegaly, sleep apneas with an adenoidectomy, inguinal and umbilical repairs.

- The patient went through inguinal hernia repair surgery at 5 months of age.
- He had been hospitalized four times due to prolonged unexplained fever, with the following test results done in October 2018:
    - An abdominal ultrasound showed an enlarged spleen with a 9.5 cm span.
    - Heart echo showed a normal result.
    - A brain and spine MRI were normal, except for a small enlargement of CSF cavities in the posterior fossa.
    - An ophthalmologist test, as well as bone scintigraphy, were both normal.
- The patient exhibited loud breathing and snoring during sleep, for which he went to a sleep laboratory showing significant sleep apneas. A subsequent endoscopy showed an adenoid with up to 90% choanal obstruction.
- In January 2019 the patient went through adenoidectomy and umbilical hernia surgery, with difficult intubation.
- A biochemical test for Iduronate-2-sulfatase has shown a decreased activity of 0.8 mmol/L/hour.
- Genetic sequencing of the IDS gene, performed in April 2019, showed the following mutation on the X chromosome:
    - P.Ala346Profs*14-Exon8
    - g.1485686 00del:(GRCH37)ChrX
    - NM_000202.5:c.1036delG
- The patient started a weekly intravenous (IV) enzyme replacement therapy (ERT) with Elaprase in May 2019.
- He is now experiencing a developmental delay, including language delay.

The patient is currently being considered for Hematopoietic Cell Transplantation (HCT), and his parents are exploring the possibility of such treatment, as well as other treatment options.

This report addresses the following questions:

Diagnosis Summary

1. What are the known risks and benefits of hematopoietic cell transplantation in a 1.9 y/o patients with Hunter syndrome (P.Ala346Profs*14-Exon8 mutation)?
2. Which innovative treatments can be effective for the treatment of a 1.9 y/o patients with Hunter syndrome in Israel and worldwide (excluding ERT)?
3. Which clinical trials worldwide are testing possible treatments for Hunter syndrome, are now recruiting (and are not focusing on ERT dosing)?
4. Who are the leading experts and leading centers in treating Hunter syndrome worldwide, that can perform HCT or other suggested treatment options?

Report Summary

הדו"ח כולל פירוט בנוגע למספר נושאים הנוגעים לטיפול במטופלים צעירים עם MPS 2 – עדויות בנוגע לקשר בין גנוטיפ לפנוטיפ, מידע בנוגע להשתלת תאי גזע המטופוייאטים, טיפולים ניסיוניים, ניסויים קליניים ומומחים בתחום. להלן תמצית המידע הרלוונטי המרכזי:

עדויות קליניות בנוגע לקשר בין גנוטיפ לפנוטיפ אצל מטופלים עם MPS 2

לא נמצאו מחקרים או מקור מידע אחר בו מתוארת המוטציה הספציפית של המטופל בהקשר של הפנוטיפ. נמצאו מחקרים בנוגע לקשר גנוטיפ-פנוטיפ ב-MPS 2 בהם נכללו מטופלים עם מוטציות השמטה (Deletion mutation) אחרות:

• במחקר מ-2017 נמצאה מגבלה קוגניטיבית בינונית-חמורה בכל חמשת המטופלים עם מוטציית השמטה (קטנה או גדולה) .

• במחקר אחר מ-2017 נכללו 15 מטופלים עם מוטציית השמטה. כל המטופלים עם מוטציית השמטה גדולה ורוב המטופלים עם מוטציית השמטה קטנה (כולם למעט אחד), היו עם פנוטיפ חמור .

השתלת תאי גזע המטופוייאטים (HSCT)

<u>יתרונות וחסרונות אפשריים של הטיפול</u>

רוב המחקרים שנמצאו הנם רטרוספקטיביים/דיווחי מקרה. יש לציין כי רוב המחקרים לא הבדילו בין מחלה חמורה למוחלשת (Attenuated).

יתרונות אפשריים של HSCT:

1. מניעת הדרדרות נוירוקוגניטיבית- אחת הבעיות המרכזיות בטיפול אנזימטי חליפי (ERT) היא שהוא אינו מסוגל לעבור דרך מחסום הדם-מוח. כיוון שבתהליך של HSCT תאי הגזע יכולים להגיע למערכת העצבים המרכזית ולהפריש את האנזים התקין, הדבר יכול לתרום למניעת ההדרדרות הנוירוקוגניטיבית. נמצאו מספר מחקרים התומכים בתיאוריה זו וביתרונות של שימוש מוקדם ב-HSCT למטרה זו. ניתן לקרוא בדו"ח באופן מפורט את מאפייני המטופלים במחקרים השונים. יש לציין כי קיימות עדויות לכך שכאשר ההשתלה מבוצעת במטופלים אצלם כבר הופיע אובדן נוירונלי משמעותי, עלולה להיות החמרה נוספת במצב הנוירוקוגניטיבי לאחר ההשתלה. במחקר יפני המוזכר בדו"ח בו בוצעה השתלה בקרב 21 מטופלים, הופיעה הדרדרות מסוג זה בקרב חלק מהם. מסקנת החוקרים הנה ש-HSCT עשויה להיות יעילה במניעת הדרדרות קוגניטיבית כאשר היא מבוצעת לפני הופעה של אטרופיה מוחית משמעותית.

2. יעילות הטיפול בכל הקשור לתסמינים שאינם נוירוקוגניטיביים- במחקר מ-2009 שכלל 8 מטופלים הייתה נסיגה של הגדלת הטחול והכבד, נראה שיפור בתווי הפנים וכן נראתה התייצבות מבחינה לבבית. במחקר מ-2014 שכלל 111 מטופלים נמצא שהטיפול יעיל באותה במידה כמו טיפול אנזימטי חליפי בשיקום הגדילה של המטופלים.

3. הימנעות מצורך בטיפול כרוני (טיפול אנזימטי חליפי) עם תופעות לוואי אפשריות .

חסרונות וסיכונים של HSCT:

Report Summary

ההשתלה כרוכה בסיבוכים אפשריים רבים, הן מוקדמים והן מאוחרים. באופן כללי הסיכונים פחתו בשנים האחרונות באמצעות מניעה טובה, מינוני תרופות מתאימים יותר והבנה טובה יותר של המנגנונים הביולוגיים הקשורים להליך. במחקר על מטופלים עם MPS 1, נמצא כי לאורך השנים נראה שיפור מבחינת שיעור הסיבוכים וכי קיים סיכון מופחת לכשל של השתל כאשר נעשה שימוש ב-Busulfan והקלטות טובה יותר שלו כאשר הוא נלקח מדם טבורי.

רוב המידע שנמצא בנוגע לסיבוכים אינו ספציפי למטופלים עם MPS 2. הסיבוכים הרלוונטיים המרכזיים הנם:

1. מחלת השתל נגד המאכסן (GVHD)- סיבוך בו תאים חיסוניים מהשתל מזהים את תאים של המאכסן כזרים ותוקפים אותם. האיברים העיקריים המעורבים הם הכבד, העור ומערכת העיכול. מחקר עדכני הראה כי השיעור של סיבוכים אלו בקרב ילדים צעירים נוטה להיות נמוך מאשר במבוגרים ובנוסף קיים מחקר המראה ירידה כללית בשיעור של סיבוכים אלו בילדים במהלך השנים. באחד המחקרים הגדולים שפורסמו בנוגע ל-HSCT במטופלים עם MPS 2, ראו כי 9% מהמטופלים סבלו ממחלת השתל נגד המאכסן ו-8% נפטרו מסיבוכים של המחלה. עם זאת יש לציין כי כל מקרי התמותה אירעו בקבוצה גדולה של מטופלים אשר עברו השתלה בין השנים 1984-2016 שהנתונים בנוגע אליהם נאספו באופן רטרוספקטיבי. בתת קבוצה המופיעה במחקר אשר טופלה בין השנים 2005-2012 והנתונים בנוגע אליה נאספו באופן פרוספקטיבי לא היו מקרי תמותה מסיבוכים של ההשתלה.

2. פגיעה ברירית הפה והלוע (מוקוזיטיס)- סיבוך זה מופיע ברמה מסוימת ברוב המטופלים העוברים HSCT. במקרים החמורים יותר הסיבוך עלול להגביל את הצריכה התזונתית.

3. זיהומים- לאחר הליך של HSCT מערכת החיסון של המטופלים מדוכאת, הן כתוצאה מהזמן שלוקח לתאי התורם להגיע לפעילות מלאה וכן עקב השימוש בתרופות מסויימות לצורך ההליך. זיהומים שונים עלולים להופיע בנקודות זמן שונות.

בימים אלו מתבצע **ניסוי קליני בשלב 2 (NCT02171104) הבודק את השימוש ב-Busulfan, ATG ו-Fludarabine לצורך קליטה של השתל במסגרת HSCT** במטופלים עם הפרעות תורשתיות שונות כולל MPS 2. ייתכן כי המטופל יתאים לניסוי המתקיים במיניסוטה בארה"ב, ויצרנו קשר עם עורכי הניסוי, טרם התקבלה תשובה. פרטי הניסוי מופיעים בו"ח.

טיפולים נסיוניים

1. טיפול ב- RGX-121- טיפול גנטי חדשני המשתמש בוירוס כנשא, על מנת להעביר את הקידוד הגנטי לאנזים החסר לתוך תאים במערכת העצבים המרכזית. במחקר פרה-קליני על עכברים נמצא כי התרופה הפחיתה הצטברות GAG בכל האיברים שנבדקו. רק חלק מהעכברים הראו הפרשה מתמשכת של האנזים במערכת העצבים המרכזית, אבל בקרב אלו שכן החוקרים הראו מניעה של הליקוי הנוירוקוגניטיבי. כיוון שטרם בוצעו ניסויים בתרופה בבני אדם אין בשלב זה מידע בנוגע ליעילות ותופעות לוואי אפשריות.

בימים אלו נערך ניסוי בתרופה בשלבים 1 ו-2 בקרב מטופלים עם MPS 2 שנועד לבדוק את בטיחות ויעילות הטיפול בתרופה. הניסוי נערך בבית החולים לילדים של פיטסבורג בפנסילבניה שבארה"ב. יצרנו קשר עם עורכי המחקר, הם השיבו כי המטופל עשוי להיות מתאים להכלל במחקר אך הדבר יצריך שהות ממושכת בארה"ב. פרטי הניסוי והחוקרים מופיעים בדו"ח.

2. הזרקה אינטרתקאלית של תאי DUOC-01-UCB-derived oligodendrocyte-like cells כתוסף להשתלת תאי גזע המטופויאטיים מדם טבורי מתורם. המטרה של הטיפול הנה לזרז הגעה של תאי התורם למערכת העצבים המרכזית על מנת לגשר על הפער בין ההשתלה וקליטת השתל ולמנוע התקדמות של המחלה. התאים מופקים מאותו דם טבורי ממנו מופק השתל. בניסויים פרה-קליניים בעכברים נראה כי הטיפול בעל פעילות בתיקון דה-מיאלינציה, אם כי יש לציין כי לא נבדק ספציפית בהקשר של MPS 2. כיוון שטרם בוצעו ניסויים בבני אדם אין בשלב זה מידע בנוגע ליעילות ותופעות לוואי אפשריות.

בימים אלו נערך ניסוי בשלב 1 הבודק את יעילות הטיפול במטופלים עם מספר מחלות מטבוליות לרבות MPS 2. המחקר נערך במרכז הרפואי של אוניברסיטת דיוק בצפון קרוליינה שבארה"ב. יש לציין כי קריטריון להכללה במחקר הנו שלמטופל לא יהיה תורם קרוב משפחה מתאים עם התאמה מלאה וכן שתהיה לו תרומה מתאימה ממקור דם טבורי. יצרנו קשר עם עורכי הניסוי, טרם התקבלה תשובה. פרטי הניסוי והחוקרים מופיעים בדו"ח.

3. נמצאו שני טיפולים חדשניים נוספים הנבדקים בימים אלו במסגרת ניסויים קליניים אולם הם מגייסים מטופלים מגיל 5 ואילך, קישורים עם פרטים בנוגע לניסויים מופיעים בדו"ח.

מומחים בתחום

1. פרופ' מונזר- מומחה ברפואת ילדים וגנטיקה מביה"ס לרפואה של אוניברסיטת צפון קרוליינה. אחד המומחים המובילים בכל הנוגע למעורבות מערכת העצבים ב-MPS 2 ובחקר הטיפול במחלה. שלחנו מייל לפרופ' מוזנר עם פרטי המטופל, טרם התקבלה תשובה.

2. ד"ר טומטסו- מנהל המרכז לדיספלזיה של השלד ואורתופדיה פדיאטרית באוניברסיטת דלאוור שבארה"ב. הוא פרסם מאמרים רבים בנוגע ל-MPS לרבות מחקרים על HSCT וניטור המחלה. שלחנו מייל לד"ר טומטסו עם פרטי המטופל, הוא השיב כי הוא סבור ש-HSCT הנה אפשרות טובה יותר מ-ERT מבחינת המטופל אולם אינו יכול להגיד בוודאות מבלי שבדק אותו. הוא הוסיף כי אינו יכול להמליץ על מרכזים ספציפיים לביצוע ההליך.

בדו"ח ניתן למצוא גם שמות של מספר מומחים נוספים וכן של מרכזים בארה"ב ובאירופה בהם בוצע HSCT במטופלים עם MPS 2.

Research Information

Introduction - the connection between the patient's genotype and phenotype

- No studies or other sources of information, where the patient's specific mutation is described by its phenotype, were found.
- Other known **deletion mutations in MPS 2**, were examined to understand their phenotype. It seems that in most cases, deletion mutations lead to a more severe phenotype:
  - A study from 2017[1] on the relationship between the genotype and phenotype, has shown a moderate to severe intellectual disability in all five patients who had a small or large **deletion** mutation.
  - Another study from 2017[2], has examined the genotype-phenotype relation and included 15 patients with deletion mutations. This study has demonstrated that in all patients with a large deletion and all but one with a small deletion mutation, a severe phenotype was witnessed.

1- Hematopoietic Stem Cell Transplantation (HSCT):

- Most of the studies found in this research are retrospective, and some are case reports of specific patients. Unfortunately, there are almost no prospective studies with available data on MPS 2 patients who went through HSCT (some patients in one of the studies presented below from 2017, were described in a prospective manner).
- Most studies performed in MPS 2 patients did not specifically distinguish those with severe disease from those with an attenuated disease. Therefore it is difficult to assess the benefit for a specific mutation. Nonetheless, when possible, this will be noted in the report.

Possible benefits of HSCT:

Preventing neurocognitive decline: One of the major issues with ERT is the inability to go through the blood-brain-barrier (BBB) and therefore affect the central nervous system (CNS) involvement. In HSCT, stem cells are seeded in the CNS after transplantation and secreting the normal form of the enzyme (Iduronate-2-sulfatase) inside the CNS, thus preventing neurocognitive decline and addressing this issue. There are several studies supporting this theory, and the benefit of early usage of HSCT:

- A recent retrospective study (2018) of four case reports[3], examined the potential of early HSCT in children (ages at transplantation; 3.9, 4, 1.6, 5.5 years) who demonstrated neurocognitive symptoms.

- All four patients demonstrated neurocognitive stabilization, and three of them showed neurocognitive and somatic (skeletal, muscular, hepatic and spleen) improvement.
- Two of these patients who had severe MPS 2, underwent HSCT at a young age and both attend a mainstream school with no additional supports.
- Another patient had developmental and language delay before the procedure and following HSCT his development has stabilized, with an unchanged MRI appearance of the brain.
- Of these children, 3 went through a transplant of unrelated umbilical cord blood (UCB) and one using matched bone marrow from a non-carrier female sibling.

- A study from 2017[4] included 146 MPS 2 patients who went through HSCT.
  - These patients generally showed either no progression and some showed improvement of lesions in MRI, while patients treated with ERT showed progressive brain deterioration with age.
  - The mean age in this study for HSCT was 5.5 years, and in this study, there is a lack of information for children under 2 years of age, although the researchers believe that there may be better results when HSCT is performed at a younger age.
  - This study retrospectively examined a group of 119 patients from other publications, and 27 "new" patients that the authors have treated and were described in a prospective manner.
- A study of 74 Japanese MPS 2 patients from 2015[5] included 20 patients who went through HSCT. Out of the 74 patients, 51 patients had a severe disease phenotype. In this study, 10 patients with a severe phenotype went through HSCT before the age of 5.
  - The study has shown a trend by which HSCT provides a higher score in activities of daily living (ADL) questionnaire compared to early ERT, in patients with severe disease. It is important to note that even though this was a trend, no significant difference was witnessed.
- A Japanese study of 21 MPS 2 patients[6] from 2012 has shown stabilization of brain atrophy in 11/17 patients who went through a follow-up MRI, and only 1/7 HSCT treated patients has experienced speech deterioration. The transplantations were performed in 1990-2003. Mean age at transplantation was 5.4 years. The 21 patient's records used in this study, were only of those who had at least 5-year survival after HSCT (5 patients did not survive).
- A single case report from 2017[7] of a 7-year follow-up of a patient with severe MPS 2, has shown improved motor function, following HSCT at 70 days of age from a not fully matched, unrelated UCB donor. On the other hand, speech development was not improved and he suffered from moderate hearing loss.

- In a study of eight MPS 2 patients[8] (5/8 with severe phenotype) from 2009, there was no prevention of neurocognitive deterioration in the four patients with a severe phenotype following the transplant. One of the patients was 16 years old at transplant, while the rest were 3-6 years old. Those with an IQ of less than 80 before the procedure have seen a drop to an IQ below 50 after a 6-year follow-up. It is believed that this may be due to lower doses than the current practice of the agent busulfan used in these cases. Busulfan is a chemotherapy agent used before the HSCT procedure, and it is believed that it has an important effect on the donor cells ability to cross the BBB[9].
- There is some evidence that when performed in patients that already present with a significant neuronal loss, there may be a decline in neurocognitive status. This was shown in the Japanese study of 21 patients[10] from 2012 mentioned above, in which deterioration was observed in six such patients.

Long term effects of HSCT on non-neurocognitive symptoms:

- In the same study of eight patients[11] from 2009, there was a resolution of liver and spleen enlargement, improvement in facial features, and lack of cardiac deterioration in all patients.
- A study from 2014[12] of 111 MPS 2 patients has shown that HSCT and ERT were equally effective in restoring growth.

Avoidance of chronic ERT related adverse reactions:

- HSCT has risks, as described below, yet it is a one-time treatment. On the other hand, ERT is a long term treatment, and holds potential risks as well, that might be avoided when using HSCT:
    - A study from 2014[13] has examined 22 MPS 2 patients that were treated with ERT. In this study 4/22 patients experienced infusion-related adverse events, such as fever, rash, and low blood pressure. In this retrospective study, no other side effects of ERT were described.
    - In a study from 2017[14] of 26 MPS 2 patients that were treated with ERT, some have shown to develop antibodies against the Elaprase treatment. This study has shown that patients with such antibodies had higher levels of glycosaminoglycans (GAG) in their urine. GAG accumulation is caused by the enzyme deficiency. Therefore, higher GAG levels in the urine may suggest the possibility of treatment tolerance. Although not statistically significant, this study has shown a possible link between these antibodies and infusion-related adverse events. On the other hand, in the 2014 study , this link was not observed.

Disadvantages and risks of HSCT:

HSCT procedure-related risks: The transplantation holds many potential early and late complications. In general, these risks have been reduced in the past years due to proper prevention, better drug dosing, and understanding of different biological mechanisms relating to the procedure.

- In MPS 1 patients [15], an increase of event-free survival rates after HSCT is seen over the years, with a 58% rate in 1994-2004, and 91% in 2005-2008. This study in MPS 1, has also shown a reduced risk for graft failure when using busulfan, and better engraftment when using cord blood rather than bone marrow.
- Most of the information about these complications is not specific for MPS 2 patients, and when specific data was found, it will be noted.
- Relevant information about possible complications:
  - **Graft-Versus-Host-disease (GVHD)**: This is a complication in which the donor's immune cells, which were transferred to the patient, recognizes the recipient cells as foreign and attacks them[16]. There are several forms of GVHD, classified according to their time of onset and their symptoms. The **acute form of GVHD** occurs in the first 100 days after HSCT, and the liver (abnormal liver function tests, usually not a severe injury), skin (a rash that may be painful), and gastrointestinal tract (diarrhea, nausea, vomiting and abdominal pain) are the organs that are most involved.
  - A recent study[17] from 2018 has shown that complication rates of HSCT are decreased in younger children (2-12 years old) compared to older patients. This study has also shown a general decline over the years of these complications in children. This study was limited to leukemia patients.
  - **Mucositis**: An inflammation of the cells lining the digestive tract. This complication happens in most patients going through HSCT[18] to a degree. In the more severe cases, this complication may limit nutritional intake.
    - In the study of four MPS 2 patients that was mentioned above, all patients suffered from either fever, rash, mucositis or blood clot. Two of these patients needed to stop the procedure to recover and then went through subsequent successful transplantation.
  - **Infections**: After HSCT, the patient's immune system is suppressed, both due to the time it takes for the donor cells to achieve full activity and because of drugs that may be used after the procedure. Different infections can occur at different time points[19] after transplantation, and the risk depends on many factors.
  - In one of the studies (2017, 146 patients[20]) on MPS 2 patients that was mentioned above, 9% of patients suffered from acute GVHD and 8% have died from associated complications. This study described 27 "new" patients that the authors have treated in a prospective manner. None of the 27 new cases died of transplantation-associated complications, and 3 of these patients (11%) had acute GVHD. It is not clear why the new patients had higher survival rates, but the authors assume it is related to better procedure outcomes in later years.

Relevant clinical trial involving HSCT:

In the case of HSCT, there is a currently recruiting phase II clinical trial[21] (NCT02171104) to test the usage of busulfan, ATG, and fludarabine-based conditioning regimens in achieving engraftment while maintaining low rates of transplant-related mortality (TRM) for patients with various inherited metabolic disorders including MPS 2.

- The patient may be eligible for this study, and an email was sent to the trial organizers. No answer was received yet.
- **Location**: Masonic Cancer Center, University of Minnesota. Minneapolis, Minnesota, United States, 55455.
- **Contact**: Kim Nelson, +1-612-273-2925, knelso62@fairview.org.

2- Innovative Treatments:

2.1. RGX-121

- **What is it?:** This new novel gene therapy drug uses a virus vector to deliver the gene encoding the deficient enzyme beyond the BBB and into the CNS cells, thus providing a permanent source of the enzyme.This therapy is aimed at **CNS involvement only** , thus does not replace ERT. The trial testing this treatment does not fit patients who already underwent HSCT, and is an alternative to transplantation.
- **Stage of development:** The drug is being tested in a phase I/II clinical trial sponsored by the drug manufacturer REGENXBIO. This clinical trial may be a suitable option for the patient.
    - REGENXBIO[22] is a company that is currently trying to develop several gene therapies. They have 4 other experimental therapies in phase I trials. REGENXBIO's gene-therapy technology was recently used in a large pharmaceutical company's (Novartis) drug, which was approved by the FDA[23] for another genetic disease (SMA).
- **Efficacy evidence:** There is not much evidence for the activity of this drug as it is in a very early stage of development. One study in mice[24] with MPS 2 has shown the drug to decrease GAG accumulation in all tested organs. Only some of these mice had sustained enzyme secretion in the CNS, but those who did had shown prevention of neurocognitive deficit. The drug was administered directly to the brain ventricles.
- **Side effects:** There is no data about adverse effects in humans, as this drug is yet to have been tested. In monkeys[25], the administration of the drug has shown to cause some mild asymptomatic toxic effect on sensory neurons.
- **How to get it?:** The drug is being offered to participants in a phase I/II trial listed below in the clinical trial section.

2.2. Intrathecal UCB-derived oligodendrocyte-like cells (DUOC-01) transplantation

- **What is it?:** DUOC-01 is a cell therapy derived and manufactured from donor cord blood. It is intended to accelerate the delivery of donor cells to the CNS, thereby bridging the gap between systemic transplant and engraftment of cells in the CNS. This will hopefully prevent disease progression. The therapy is administered intrathecally (into the spinal canal). Both the DUOC-01 cells and cells used for HSCT will be derived from the same UCB donor unit.
- **Stage of development:** The drug is being tested in a phase I clinical trial performed at Duke University. This clinical trial may be a suitable option for the patient.
- **Efficacy evidence:** In a pre-clinical trial[26], the drug has shown to promote remyelination (the creation of new myelin sheath around axons in the CNS, which may be lost in different MPS syndromes[27], causing neuro-cognitive symptoms). A study in mice[28] has shown the drug to have an activity in correcting demyelination, though in this setting MPS was not specifically tested.
- **Side effects:** There is no data about adverse effects in humans or animal models.
- **How to get it?:** The drug is being offered to participants in a phase I trial listed below in the clinical trial section.

Other Novel Treatments:

- Only a few novel and innovative treatments are currently being tested for MPS 2 worldwide.
- On top of the treatments presented above, two[29] additional treatments[30] that are being examined in clinical trials were found, yet both are recruiting only patients older than 5 years of age:
  - Zinc Finger Nuclease[31] SB-913[32] (NCT03041324) - Link.
  - Adalimumab[33] (NCT03153319) - Link.

3- Clinical Trials:

Clinical trials = Trials to evaluate the effectiveness and safety of medications or medical devices by monitoring their effects on large groups of people.

- Listed below are the two actively recruiting clinical trials that may be suitable for Hunter syndrome patients, aged 1.9 years that is currently receiving ERT, worldwide.

Research Information

Therapy tested	Trial description	Therapy description	Phase and placebo	Location, contacts and next steps
RGX-121	This study will evaluate the safety and efficacy of treatment with RGX-121 in MPS 2 patients, for up to a total of 104 weeks. * This trial does not fit patients who underwent HSCT.	RGX-121 is a new novel gene therapy drug that uses a virus vector to deliver the gene encoding the deficient enzyme beyond the BBB and into the CNS, thus providing a permanent source of the enzyme. It is further described in the innovative treatments section above.	Phase I/II No placebo	**Location**: Children's Hospital of Pittsburgh - UPMC: Program for Neurodevelopment in Rare Disorders, Pittsburgh, Pennsylvania, United States, 15224. **Contacts**: Jodi Martin - Research Coordinator, +1-412-692-6351, sausjl@upmc.edu Dr. Maria Escolar - Principal Investigator, maria.escolar@chp.edu Link NCT Number: NCT03566043 * An e-mail has been sent to Dr. Escolar about the possibility of enrolling the patient. The researcher has informed us that the patient may indeed be eligible for the trial, but it will require a long stay in the US.
DUOC-01	This study will evaluate the safety and feasibility of intrathecal administration of DUOC-01 as adjunctive therapy in patients who are undergoing standard treatment with unrelated umbilical cord blood transplantation (UCBT). * Special requirements: Patients who have a suitable fully matched, non-carrier sibling or related bone marrow donor can not join the trial. Patients who join the trial must find their UCB donor and have an available, suitably matched, banked UCB unit in a two-compartment configuration.	DUOC-01 is a cell therapy derived and manufactured from donor cord blood. It is intended to be used as a bridging therapy to provide functional enzyme in the CNS after systemic transplantation and is administered intrathecally. It is further described in the innovative treatments section above.	Phase I, No placebo	**Location**: Duke University Medical Center, Durham, North Carolina, United States, 27705 **Contact**: Jennifer Baker, +1-844-800-2673, cordbloodtherapyinfo@dm.duke.edu Link NCT Number: NCT02254863 * An e-mail has been sent to the research coordinator about the possibility of enrolling the patient, and we are waiting for a response.

Clinical trial phase definitions:

Phase	Description
I	Phase I is the first stage in the clinical development of a medicinal product. It is to ensure a treatment is safe for people to take, rather than to try to treat a condition. These trials are very small, (typically around 30 people), and usually involve healthy volunteers or sometimes patients.
II	Phase II aims to investigate the safety and effectiveness of a potential therapy. Usually between 100 and 300 people will be enlisted to take part with the aim of determining whether the treatment will be safe and effective to treat a condition.
III	If previous trials have indicated a treatment is safe and that it also shows promise in being able to treat a condition, phase III clinical trials begin. These involve large numbers of participants, usually from several hundred to several thousand subjects, and are often spread between different hospitals and countries. If these trials show that a drug is safe and effective, the manufacturers can apply for a marketing authorization.
IV	Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

4- Experts & Clinical Centers:

4.1. Experts

This list of experts was assembled by searching for top-rated doctors from well-known hospitals around the world, which answer the following criteria:

- Years of experience in treating MPS 2, especially with HSCT.
- Research expertise including clinical studies.
- Papers published in the last years which are relevant to the patient's condition.

The expert list contains the two most relevant experts, who met all the criteria above. A few lead experts have come up during the research process, yet they were not fully suitable for this list. These experts include:

- Prof. Michael Beck - consultant at the Institute of Human Genetics at the University of Mainz[34].
- Prof. Nathalie Guffon - metabolic disease expert at CHU de lyon[35], France.
- Dr. Simon Jones - Consultant in pediatric inherited metabolic disease and senior lecturer at the University of Manchester[36].
- Prof. Barbara K Burton - Professor of pediatrics and genetics at the Northwestern School of Medicine[37].

Name	Description	Location and contacts
Joesph Muenzer, MD[38]	Professor Muenzer is an expert in pediatrics and genetics at the University of North Carolina (UNC) School of Medicine. Professor Muenzer is one of the leading experts in the field of CNS involvement in MPS 2, and is the main researcher of new treatments for the disease. He has led many clinical trials with a lot of publications[39] on novel gene therapy, intrathecal drug delivery and new forms of ERT. * An e-mail was sent to Prof. Muenzer with the patient's details in the hope he has more insights and recommendations for future treatments.	Location: 117 Medical School Wing E CB# 7487 Chapel Hill NC 27599-7487 Phone: tel:+1-919-966-1447 Mail: muenzer@med.unc.edu Link
Shunji Tomatsu MD. PhD.[40]	Dr. Tomatsu is the director of the Skeletal Dysplasia Center and Pediatric Orthopedic Surgery at the University of Delaware. His research has been focused on different types of MPS, including Hunter syndrome. Dr. Tomatsu has published many articles[41] on MPS in general and specifically on Hunter's, with publications including studies on HSCT and monitoring of the disease. * An e-mail was sent to Dr. Tomatsu with the patient's details in the hope he has more insights and recommendations for future treatments. Dr. Tomatsu answered that he believes HSCT is a better option than ERT, yet he cannot say for sure without seeing the patient. He also explained he cannot recommend any specific centers for the	Location: 1600 Rockland Rd., Wilmington, DE. 19899-0269 Phone: +1-302-298-7336 Mail: stomatsu@nemours.org Link

4.2. Clinical Centers

- We didn't find any information about the number of Hunter syndrome patients treated with HSCT in specific centers. As a result, there is also a lack of data regarding success rates and outcomes of this procedure in centers that are known to have used HSCT in such patients.
- The only information available is the names of four hospitals in the US[42] which performed HSCT in Hunter syndrome patients, as well as one hospital in Europe[43]:
    - UPMC Children's Hospital of Pittsburgh (Link).
    - Dana Farber Cancer Institute - Department of Pediatric Oncology (Link).
    - Duke University Medical Center - Pediatric Blood and Marrow Transplant Program (Link).
    - Cincinnati Children's Hospital Medical Center (Link).
    - Saint Mary's Hospital in Manchester, England (Link).

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Doctor's Letter

Dear Dr.

1. Could HSCT be a treatment option for this patient?

2. Could the clinical trials described in the report be an option for this patient (RGX-121- NCT03566043 and DUOC-01- NCT02254863)?

Thank you for taking the time to respond.