DATASPACE 4HEALTH
LUXEMBOURG

FUNCTIONAL PROCESSES - RESEARCH POC

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This document is intended to be published on the Dataspace4Health website.

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LIST OF ABBREVIATIONS

CFB	Centre François Baclesse
CGP	Comprehensive Genomic Profiling
DE	German
DSP	Dossier de Soin Partagé (shared electronic health record)
DS4H	Dataspace4Health
DT	Digital Twin
EHR	Electronic Health Record
ESMO	European Society for Medical Oncology
FR	French
GDPR	General Data Protection Regulation
GLP-1	Glucagon-like peptide-1
GP	General Practitioner
HbA1c	Hemoglobin A1c
HCP	Healthcare Professional
INC	Institut National du Cancer (National Cancer Institute)
LB	Luxembourgish
LIH	Luxembourg Institute of Health
LNDS	Luxembourg National Data Service
LNS	Laboratoire National de Santé (National Health Laboratory)

MTB	Molecular Tumor Board
NCP	National Center of Pathology
NGS	Next Generation Sequencing
PNC	Plan National Cancer (National Cancer Plan)
PoC	Proof of Concept
RCP	Réunion de Concertation Pluridisciplinaire (Multidisciplinary Consultation Meeting)
WGS	Whole Genome Sequencing

EXECUTIVE SUMMARY

- **Purpose of the document:** To define the functional processes that enable the Dataspace4Health (DS4H) framework to be deployed in real-world clinical settings. It bridges the gap between the technical- and the practical workflows of healthcare professionals, demonstrating how secure and compliant data (re)use can enhance both care delivery and research.
- **Key Objectives:** To outline the current- and envisioned future processes for the two use cases, namely how digital tools like the Digital Twin (DT) and envisioned Molecular Tumor Boards (MTBs) can support personalized, predictive and data-driven care (including patient consent management and data anonymization/pseudonymization).
- **Strategic Importance:** To enhance clinical outcomes through personalized care and early complication prevention, to empower healthcare professionals with decision support tools and predictive analytics and to facilitate research and innovation by enabling compliant secondary use of health data.

1. INTRODUCTION

The aim of this deliverable D6.2 is to define functional processes that bridges the technical data workflows described in D6.1 with real-world medical- and care practices within a hospital. The objective is to demonstrate how both the technical infrastructure and clinical workflows can interact in production.

This document focuses on the two use cases – diabetes in regards to the DT and oncology in regards to the MTB – to illustrate how the DS4H framework can be utilized to enable secure and legal (re)use of patient data for care optimization and research. Both use cases integrate patient consent processes and data anonymization/pseudonymization.

This document also outlines the current state of data and care workflows, the envisioned target processes and the requirements needed to enable the Proof of Concept (PoC) in a standard care setting.

This document is divided into two sections, for each use case respectively.

2. DIABETES USE CASE

This chapter will describe the current diabetes process in a simplified way, followed by the envisioned future process in which the DT is utilized. Finally, this chapter will demonstrate different proposals to obtain and manage patient consent to allow usage of the DT.

2.1 CURRENT DIABETES PROCESS

This subchapter will provide a simplified overview of the current medical- and care processes for the treatment of a diabetic patient.

The process starts when a patient presents with diabetic symptoms (such as increased thirst, frequent urination, fatigue, blurred vision or unexplained weight loss) [1]. The patient is either referred by a General Practitioner (GP), or directly requests a consultation with a medical specialist.

During the initial consultation, the medical specialist examines the patient and prescribes specific laboratory tests (like Hemoglobin A1c (HbA1c), C-peptides, antibodies, Oral Glucose Tolerance and fasting blood glucose to measure blood glucose levels) [2]. Based on both the physical examination and the results from the laboratory testing (including additional testing for e.g., cholesterol, creatinine, microalbuminuria, urine test etc.), the medical specialist will establish a diagnosis (e.g., pre-diabetes, Type 1 Diabetes, Type 2 Diabetes, gestational diabetes etc.) [3] [4].

After establishing the diabetic diagnosis, the medical specialist assesses the severity, progression and the presence and/or risk of complications in order to guide treatment decisions. This assessment may involve referrals to specialists such as ophthalmologists for retinal screening, cardiologists, nephrologists for kidney evaluation and neurologists assisted by a foot specialist for nerve and foot assessments [5]. Risk calculators and scoring systems may be used to estimate cardiovascular risk and guide preventive strategies [6]. Possible diabetic complications include (but are not limited to) microvascular complications (such as retinopathy, nephropathy and/or neuropathy), macrovascular complications (such as cardiovascular and/or peripheral artery disease) and/or diabetic foot ulcers [7].

Then, in collaboration with the patient, a treatment plan is formulated. The treatment plan typically consists of a combination of lifestyle modifications (such as weight loss through improved physical activity, dietary changes, smoking cessation, etc.), oral medications (e.g., Metformin), injectables (e.g., Glucagon-like peptide-1 (GLP-1) agonists such as Semaglutide), multiple daily insulin injections and/or an insulin pump [8] [9]. The choice of therapy depends on factors such as the type of diabetes, HbA1c level, presence of comorbidities (e.g., heart failure, chronic kidney disease) and risk of complications [10]. Additionally, the treatment plan will also include how the follow-up care for the patient will be organized – including the frequently and location of care (e.g., at a diabetes clinic, diabetic foot clinic, through hospitalization and/or with the general practitioner). The frequency of follow-up visits may vary from every few weeks (e.g., during initial stabilization) to every 3–6 months for routine monitoring [11].

Afterwards, the patient (and potentially family member(s)) receives information, is educated and coached to learn how to live with the diabetes diagnosis, adhere to the established treatment plan and lifestyle changes. For this, different Healthcare Professionals (HCPs) are involved, such as nurses (specialized in diabetes and wounds), dieticians, podiatrists and psychologists [12]. This includes setting up physical activity and dietary plans, education on how to administer medication and/or set-up, adjust and use devices and reviewing and interpreting subsequent data. Education may also cover topics such as carbohydrate counting, insulin titration, recognizing signs of hypo- and hyperglycemia, foot care and coping strategies for chronic illness, as well as adopting a balanced and appropriate diet. Peer support groups and digital tools (e.g., mobile apps, continuous glucose monitoring systems) may also be introduced to enhance self-management [13].

Based on the evaluation of daily or continuous blood glucose monitoring and periodic laboratory testing (e.g., HbA1c), together with physical examinations, the established treatment plan can either be maintained or adapted during each follow-up visit. Adjustments may include intensifying therapy, switching medications, addressing side effects or managing emerging complications [14].

Currently, the use of digital tools is fragmented, data collected from devices is often not integrated into the hospital's Electronic Health Record (EHR). There is no dynamic link between treatment adjustments, complication prediction and real-time data analysis. This limits the ability to personalize care over time and reuse collected data for secondary or decision support purposes.

While the current care process is medically structured, it remains largely reactive to advanced data-driven decision-making. This highlights the need for a more integrated, intelligent and patient-centered model, such as that envisioned by the DT concept.

2.2 ENVISIONED FUTURE PROCESS IN PRODUCTION

The envisioned future process, in which medical- and care personnel will be able to utilize the DT concept for the treatment and education of diabetic patients, is described in this subchapter. This includes both a detailed description of the anticipated benefits in using the DT concept in the diabetes care process with concrete examples, as well as a section outlining where, when and by whom the DT concept could be used in the existing process.

The integration of DT represents a shift from reactive care to more predictive, personalized and data-driven approach. The DT acts as dynamic, continuously update the model of the patient, build from multiple data sources and used to simulate outcomes, support clinical decisions and inform patient care.

The envisioned process includes the following:

- **Data integration:** At the time of diagnosis, clinical data and laboratory analysis are produced and consolidated in the DT. This includes structured data. The DT is initialized using this reference data to create a virtual representation of the patient's current state of health.
- **Personalized simulation and prediction of complications:** The DT uses clinical models to simulate disease progression under different treatment strategies. For example, it can predict the long-term effect of introducing a GLP-1 agonist on HbA1c levels or estimate the risk of cardiovascular complications if glycemic control remains inadequate. These simulations enable clinicians to develop personalized treatment plans based on predicted individual outcomes rather than general guidelines.
- **Support in decision-making:** The DT serves as a support aid in decision-making during consultations, allowing practitioners to visualize and explain future scenarios with patients. This helps patients to gain a better understanding of how lifestyle changes or treatments may impact their condition. The DT enables personalized support and education.
- **Continuous monitoring and personalized care:** As treatment progresses, new data is integrated into DT. The model continuously updates and detects deviations when care adjustments are needed (e.g., early signs of complications). This allows HCPs to intervene earlier and to get supported by data-informed decisions.
- **Data-driven reviews:** The DT gives a shared view, accessible by only authorized HCPs involved in patient care. It will ensure consistency and support integrated care based on shared data.
- **Consent-driven data use:** Consent allows patients to give, modify or withdraw their permission for the use of their data. Data for secondary use is only made available in anonymized/pseudonymized form.
- **Expected outcomes and value:** This future process aims to improve clinical outcomes and patient care through personalized monitoring. It will allow the prediction and prevention of complications. It will enable secondary use of data in a compliant and structured manner. Finally, it will establish the foundation for scalable and replicable digital care models across other chronic conditions.

2.2.1 BENEFITS OF UTILIZING THE DT CONCEPT IN DIABETES CARE

By integrating the DT technology in the current diabetes care process – and enabling its use by both medical specialists and nurses – the quality and personalization of care could be significantly

enhanced. A DT is a dynamic, virtual representation of a patient that continuously evolves by integrating real-time data from the EHR (including laboratory results), lifestyle information and potentially wearable devices. This virtual model then enables HCPs to simulate, predict and personalize care based on a patient's unique profile and characteristics.

One of the main difficulties in current diabetes care is the limited consultation time available that HCPs have during clinical visits to discuss prevention and long-term risk management. The DT would address this gap by acting as a clinical decision support system that can synthesize patient-specific data with insights from publicly available medical literature and clinical guidelines. As a result, this system would then be able to support HCPs in making evidence-based, personalized treatment decisions.

For medical specialists, this allows for precision prevention by identifying which patients are at higher risk for complications like nephropathy, retinopathy, neuropathy or cardiovascular disease, enabling early intervention with targeted strategies. Moreover, the system can suggest alternative treatment options to medical specialist if a patient is unwilling or unable to follow a specific recommendation. For instance, if a patient declines insulin therapy, the DT may propose a combination of oral agents or GLP-1 receptor agonists based on outcomes observed in similar patient profiles. Similarly, the medical specialist can interact with the DT to simulate outcomes and formulate alternative treatment options when a patient refuses to take medication altogether.

For nurses, the DT would serve as a valuable tool to support patient education, behavioural coaching and ongoing monitoring. Nurses can use the DT to tailor educational content, set realistic goals and provide feedback that is both data-driven and empathetic. For example, the DT can simulate the impact of various lifestyle changes or treatment options on a patient's future health trajectory. This allows the patient to visually understand the potential benefits of weight loss, dietary adjustments, increased physical activity or (improved) medication adherence. By illustrating the consequences of different choices, the DT becomes a powerful tool for therapeutic education and behavioural motivation.

In summary, utilizing the DT concept would allow to transform diabetes care from reactive to proactive, from generalized to personalized and from fragmented to integrated. It empowers both HCPs and patients to make more informed and better decisions, ultimately aiming to improve outcomes and quality of life.

2.2.2 PLACE OF THE DT IN CURRENT DIABETES CARE PROCESS

To leverage the benefits of the DT in diabetes care, it is essential to define where in the care process the DT can be applied, when it can be used and by whom. The DT is not a standalone tool, but rather a dynamic decision support system that can be used across multiple stages of the patient journey, aiming to enhance clinical decision-making, improve patient education and support the early identification and prevention of complications.

The first moment where the DT can be utilized in diabetes care is during the initial consultation after diagnosis, by a medical specialist. Based on a patient's unique characteristics, by comparing them with similar profiles, the medical specialist is able to simulate the expected disease progression. This helps in formulating the most appropriate initial treatment strategy and the early identification of individual risk factors for complications. The DT can simulate the effects of different medication, lifestyle changes and patient preferences, thereby enabling the co-creation of a personalized treatment plan. This, in turn, allows for and promotes shared decision-making and improved adherence to the formulated treatment plan.

Next, the DT can be used for patient education and coaching during an education session after a treatment plan has been established and during follow-up visits by nurses. The DT can visually demonstrate the impact of lifestyle changes (e.g., diet, exercise, medication adherence etc.) on long-term health outcomes. As a result, the DT becomes a motivational and educational tool, helping patients understand the consequences of their choices in a personalized and engaging way.

Later in the care pathway, the DT can be used by all HCPs (both medical specialists and nurses) during routine follow-up intervals or when clinical deterioration is suspected, to continuously assess the patient's risk of complications using up-to-date data. The DT can flag deviations from expected trajectories, allowing timely interventions as well as the exploration and simulation of treatment adjustments.

While the current use case for the DT focuses on supporting medical specialists and nurses in clinical decision-making, patient education and complication prevention, the potential applications of the DT extend beyond this scope. Additional use cases that are foreseen to further enhance diabetes care and professional development are:

- **Junior medical specialists, nurses or medical students:**
  The DT can serve as a simulation-based training platform with the virtual patient profiles, allowing users to interact with these virtual patient profiles and explore diverse clinical scenarios, test treatment strategies and observe simulated outcomes without risk to real patients. This educational use supports professional development and helps bridge the gap between theoretical knowledge and practical application.
- **GPs:** In a decentralized care model, GPs could use the DT to monitor and follow-up on stable diabetic patients at the primary care level. This shift would improve accessibility and continuity of care and reduce pressure on overburdened specialist centers. By integrating the DT into primary care workflows, healthcare systems can improve efficiency and promote more equitable access.
- **Dietitian:** A promising application of the DT lies in personalized nutrition support. By integrating dietary data, glycemic responses, lifestyle behaviors and physical activity, the DT can function or aid as a virtual nutrition expert. It can provide tailored nutritional advice, recommend personalized meal plans and support patients in making evidence-based dietary choices. This could help optimize metabolic control and promote long-term adherence.
- **Telemedicine and remote care teams:** Looking ahead, the DT could be seamlessly integrated into telemedicine platforms. This would allow healthcare providers to monitor patients remotely by e.g., obtaining (health) data from (patient) equipment and to intervene proactively when deviations from expected health trajectories are detected. Such integration of different systems and applications would allow for continuous remote monitoring, timely adaptation of treatment plans and early identification of warning signs. This would in turn reduce the need for in-person visits, improves continuity of care and enable early detection and prevention of complications.

Finally, the DT can be integrated at multiple stages of the diabetes care pathway from diagnosis to follow-up, supporting personalized treatment planning, patient education and proactive complication management. By complementing the work of various HCPs and facilitating data-driven support, the DT offers substantial value across the continuum of care. However, to ensure its responsible and sustainable use, it is important to define how sensitive health data are collected, processed and shared. This includes critical aspects such as patient consent, as well as data anonymization and pseudonymization, which are essential prerequisites for the ethical and regulatory integration of the DT into clinical practice.

2.3 PATIENT CONSENT & DATA ANONYMIZATION AND PSEUDONIMIZATION

The DT relies on a wide range of personal health information including clinical records, lifestyle data and potentially real-time inputs from wearable devices to simulate, predict and personalize care. Given the sensitive nature of this data, obtaining patient consent is mandatory before data processing activity within the DT framework. Two distinct categories of data use are recognized:

- **Primary use:** Directly use of patient data during the consultation with HCPs to support personalized clinical decision-making and patient education.
- **Secondary use:** Data used beyond individual care delivery, such as for algorithm training, model validation, performance optimization or research.

In both cases, data subjects must be fully informed about how their data will be used, who will access it and what safeguards are in place. Moreover, patients must retain the right to withdraw their consent at any time, without consequences for the care they receive.

When data are used for secondary purposes, additional protection measures such as pseudonymization or anonymization must be applied to preserve privacy and ensure compliance with data protection regulations. These aspects are critical to building patient trust and enabling the ethical, legal and sustainable implementation of DT technologies in healthcare.

2.3.1 CONSENT FOR PRIMARY USE OF DATA

Primary use refers to the application of the DT during a clinical consultation to support real-time decision-making and patient engagement. In this context, the DT uses the patient's own data to simulate disease progression, evaluate treatment options and visualize the impact of lifestyle changes.

For primary use of data, the patient would need to provide consent prior to, or during the consultation. As the DT will be an addition to standard of care, this will be through an opt-in process. The data involved may be in identifiable or pseudonymized form and typically include EHRs, laboratory results, clinical observations and lifestyle-related inputs.

These data are used only within the context of the individual's care and are not reused for algorithm training, system development or research purposes. This ensures strict adherence to the principle of data minimization.

Patients must also be informed that they retain the right to withdraw their consent at any time, without any adverse consequences for the care they receive. The processing of data for primary use is thus fully compliant with data protection frameworks such as the GDPR Article 9(2)(a) concerning the processing of sensitive health data based on explicit consent. This type of consent could be integrated into a standard consent process for treatment and care and must be handled with controlled access, secure storage and compliance with hospital clinical governance policies.

2.3.2 CONSENT FOR SECONDARY USE OF DATA

In addition to supporting individual care (primary use of data), patient data can be used to train, validate and improve the DT model. This is defined as secondary use of data and requires explicit, separate consent from the patient. As for primary use of data, the patient need to provide consent through a clearly defined and completely voluntary opt-in process for secondary use of their data.

Data used for secondary purposes which refers to the utilization of patient data beyond direct care delivery for example, for algorithm development, performance evaluation, system optimization or (medical) research. Data used can be either in anonymized or pseudonymized form:

- **Anonymized data** are processed in such a way that no individual can be identified, either directly or indirectly. This provides the strongest level of privacy protection, as the data cannot be tracked back to a specific patient. However, anonymization prevents the establishment of feedback loops from individual outcomes, meaning that the data shared with the DT outside of the patient consultations cannot be used to trigger early interventions or personalized updates.

- **Pseudonymized data**, in contrast, does allow the linkage through attributed identifiers. This allows for feedback loops, longitudinal performance monitoring and model evaluation on specific patient groups, while maintaining a layer of identity protection.

To ensure privacy and legal compliance, pseudonymization processes *could* be handled by a trusted third party, such as the Luxembourg National Data Service (LNDS). This independent intermediary would ensure that patient identity is decoupled from the data, thereby reducing the risk of re-identification and reinforcing public trust.

Patients must be clearly informed about:

- The specific scope and purpose of secondary data use
- The technical and organizational safeguards in place to protect their privacy
- Who will have access to the data and under what conditions
- The fact that participation is entirely voluntary and can be withdrawn at any time, without any impact on the patient's ongoing medical care

Sharing data for secondary purposes allows for more data to be collected on a continuous basis which in turn enables the development of a more robust predictive model and thus enhances future patient care.

2.3.3 CONSENT MANAGEMENT

As previously described, a patient can give no consent, consent for primary use of data, secondary use of data or a combination of both. To ensure transparency, compliance and patient empowerment, a structured consent management system must be implemented. The consent management system should include, but not be limited to:

- **Modular consent forms:** Patients must be able to provide separate and specific consent for primary use, secondary use or both. For secondary use, the form should allow patients to choose between whether their data is shared in an anonymous- or pseudonymous format.
- **Digital consent tracking:** Consent status should be digitally recorded and integrated into the patient's EHR, enabling real-time access and updates by HCPs.
- **Clear communication:** The consent form must be written in plain language and may include visual aids (e.g. infographics or image) to ensure patients fully understand how the DT works, why their data are needed, how they will be used and what privacy safeguards are in place.
- **Consent renewal and withdrawal options:** Patients must be informed of their right to review, modify or revoke their consent at any time, without any impact on the quality of care. Instructions for exercising these rights must be clear and accessible.

- **Audit trails and access logs:** To ensure accountability, traceability and compliance with data protection regulations, all consent activities (including date, version, signatory, access and updates) must be logged.
- **Voluntariness and neutrality**: The form must emphasize that consent is strictly voluntary (opt-in) and that the patient's decision whether to give or withhold consent will not affect the quality of care received. HCPs must not influence the patient's decision.
- **Eligible signatories**: Consent may be given by the patient themselves or, in the case of minors or legally incapacitated individuals, by an authorized legal representative (e.g., a parent, legal guardian or designated caregiver), as defined by applicable national laws.
- **Electronic capture and authentication**: Instead of relying solely on paper-based forms, consent could be captured electronically via secure digital means, such as a QR code-based e-signature or biometric confirmation. This would enhance traceability, reduce administrative burden and facilitate integration into EHR systems.
- **Consent-driven data access controls**: The EHR system should include tick-box options corresponding to the different levels of consent (primary, secondary, both or no consent). Depending on the selected option, the system should, by design, allow, restrict or prevent data extraction and access by the DT accordingly.
- **Data extraction on patient request**: Patients should have the right to request access to the data processed by the DT and to receive a copy of this data in a structured and readable format (in accordance with GDPR Article 15 and 20). Procedures must be in place for patients to initiate such requests and receive timely responses.
- **Archiving and retention policy**: Consent forms and associated metadata must be securely archived in compliance with national and EU regulations. A defined retention period should be set (e.g., 10 years after consent withdrawal or last use), after which data and consent records should be deleted or anonymized, unless otherwise justified by law.

In Luxembourg, this would concretely mean that the envisioned consent form for sharing health data for use of the DT contains a section to consent to sharing data for primary use, consent to sharing data for secondary use or consent to sharing data for both primary- and secondary use. In case of consent for secondary use, the form should allow patients to choose between whether their data is shared in an anonymous- or pseudonymous format.

The consent form shall be written and made accessible to patient in (at a minimum) all official languages of the country (LB, FR & DE), as well as English. The consent form shall contain clear information on how the data will be used, why the data is needed (including potential benefits), describe what risks are involved (e.g., possible data breaches) and what safeguards are in place to protect patient privacy. All information shall be presented in layman's terms, ensuring it is easily understandable by all patients, regardless of (health) literacy.

The form shall also emphasize that consent is voluntary and on an opt-in basis and that the decision to give or withhold consent will not affect the quality of care received. The medical specialist cannot influence the patient to give or withhold consent. It must clearly describe the patient's right to review, modify or revoke consent at any time and provide instructions on how to do so.

From a technical perspective, it is envisioned that – if voluntarily obtained – the signed consent form is uploaded to the patient's record. The diabetes record within the EHR shall be updated to allow for the different consent options (primary, secondary, both or no consent) as tick-box options. Depending on if and what tick-box is selected, by design the diabetes record could (should) be created in such a way that it would allow, restrict or prevent the different data extraction respectively (e.g., if no tick-box is selected or the "No consent" tick-box is selected, the DT would by design not be able to access this specific's patient data).

Another (long-term) proposal would be to have this consent management system (additionally) within the Dossier de Soin Partagé (DSP - shared electronic health record), in line with the proposal as outlined in the WP1 deliverable D1.1_D1.2. Consent management must go beyond the mere collection of signatures. It requires a dynamic, patient-centric governance model that ensures legal compliance, traceability, respect for patient autonomy and implementing modular, multilingual and interoperable consent processes supported by technical safeguards and trusted third-party.

3. ONCOLOGY USE CASE

This chapter will describe the current organization of MTBs in Luxembourg and their identified limitations (e.g., related to data sharing and genomic testing). Precision oncology increasingly relies on comprehensive genomic testing and the integration of molecular data into clinical decision-making. MTBs therefore play a crucial role in bridging clinical expertise and molecular knowledge, enabling more personalized treatment strategies. This chapter will describe the current organization of MTBs, as well as propose suggestions to improve and subsequently present the envisioned future process.

3.1 CURRENT ORGANIZATION OF MTBS

In line with the *Concept National Réunion de Concertation Pluridisciplinaire en Cancérologie* (RCP – multidisciplinary team meetings in oncology), RCPs are regularly organized within Luxembourg.

RCPs are organized both on an institutional level within individual hospitals with additional participation from key clinical stakeholders such as the Laboratoire National De Santé (LNS – National Health Laboratory) and the Centre François Baclesse (CFB – national center for radiotherapy), as well as on a national level for more rare cancer types, such as sarcomas and germ cell tumors, advanced hematology, neuro-oncology, gynecology and for other rare or complex types of cancers. These meetings bring together a multidisciplinary team including oncologists, surgeons, radiotherapists, radiologists, pathologists and other specialists as required. Their main objective is to establish a consensus-based treatment strategy according to clinical guidelines, while also providing a forum for discussing complex cases that require individualized approaches. The frequency of RCPs may vary depending on the hospital and cancer type, but they generally take place on a weekly or bi-weekly basis to ensure timely decision-making for patient care.

In Luxembourg, MTB meetings are organized at a national level, under the responsibility of the Institut National du Cancer (INC – National Cancer Institute), in alignment with the objectives of the national oncological strategy as outlined in the Plan National Cancer (PNC – National Cancer Plan). These MTBs aim to provide expert guidance for oncologists with patients with complex clinical situations who may benefit from advanced molecular analysis, particularly when standard treatment options have been exhausted or are not appropriate. Unlike standard RCPs, MTBs specifically focus on patients who may benefit from molecularly guided treatment decisions. The boards integrate expertise not only from clinicians, but also from molecular biologists and geneticists. Their role is to interpret genomic results, assess the clinical relevance of detected variants and provide therapeutic recommendations, including potential access to clinical trials. As a result, patients with certain cancer mutations may be considered for targeted therapies or precision medicine protocols following MTB discussion.

A patient first needs to be discussed in an RCP (regardless if this is local within a single hospital, or nationally) prior to being referred to the national MTB.

The request for Comprehensive Genomic Profiling (CGP) must be formally endorsed by the RCP, based on a documented medical rationale and a reasonable expectation of clinical benefit. Patient consent is required at two stages of this pathway:

- A first consent, to allow for the discussion of the patient's case during the RCP
- A second consent, prior to referral to the MTB and before any genomic testing can be initiated

Once these conditions (consent obtained, case discussed in an RCP and the request for enrollment in the national MTB and subsequent CGP is endorsed by the RCP with medical need/expected benefit for the patient) are met, the following form needs to be filled by the treating physician "*Request for comprehensive genomic profiling and discussion by the molecular tumor board"* and submitted to both the INC and LNS.

In the request form, the following information needs to be (manually) collected and (manually) filled:

- Patient information
  - First name
  - Last name
  - Date of Birth: as DD/MM/YYYY
  - RPNI (national registry number)
  - Sex: as F (Female) or M (Male)
  - Hospital reference
  - Phone number
  - Pathology Specimen to be tested (if known, also provide the LNS National Center of Pathology (NCP) case number)
- Patient history and indication for testing (incl. a succinct medical description of the patient history and current state)
  - Indication for CGP
  - Cancer type
  - Status at the time of testing (as tick-box): Metastatic, Relapsed or Treatment Refectory
  - Prior / current targeted therapies
  - Which RCP endorsers this request for CGP: RCP name and date
- Threating physician information
  - Treating physician name
  - Phone
  - Fax
  - E-mail
  - Physician code
  - Facility / Address
  - City
  - Postal code
  - Country
  - Additional physician(s) to be copied
- Physician signature and consent
  - Signature of treating physician
  - Printed name of treated physician
  - Date: as DD/MM/YYYY

Additionally, LNS is afterwards responsible for filling the following section within this form:

- Specimen
  - NCP pathologist responsible for the case
  - NCP case number
  - Bloc number
  - Fixation time (as tick-box): <6h, 6-72h or >72h
  - Specimen type (as tick-box): biopsy, surgical resection, punction or cytology
  - Specimen features (as tick-box): limited amount, necrosis or decalcification
  - Tumor cell content (as %)

When the patient is enrolled for the MTB, for the molecular testing itself, Next Generation Sequencing (NGS) technology is used to analyze their sample by either:

- OncoDEEP analysis, performed by OncoDNA
- CGP using the Illumina TruSight Oncology 500 Assay, performed by the LNS

The MTB typically take place every 4 to 6 weeks, at a fixed time (Fridays between 15-16h), via videoconferencing using Webex. Each case is introduced by the treating physician and participants share their screen during the meeting to display information.

Typically, the following specialties are present during a MTB meeting:

- Moderating physician (of the MTB)
- Treating physician of the patient(s) discussed
- Oncologist
- Molecular biologist (LNS)
- Anatomopathologist (LNS)
- Physician specialized in molecular diagnostics (expert from abroad)

MTB meetings are scheduled 3 to 4 months in advance. Typically, patients need to be registered to a specific MTB 16 days in advance.

In preparation to the MTB, a specific report is prepared per patient by the INC, for which different actors (such as the treating physician from the hospital, as well as the molecular geneticist from the LNS) need to (manually) collect and provide (patient) information using Regify:

- Patient name
- Patient age
- Patient ID
- Presented by (name of treating physician)
- Date the consent was signed
- Initial diagnosis
  - Diagnosis date
  - Clinical diagnosis
  - Primary tumor site
  - Known metastatic site
  - List of sites
  - Clinical staging at diagnosis
- Histology
  - Date of biopsy/surgery
  - Histological diagnosis
  - Biomarkers tested (yes/no)

    - Details
- Molecular diagnostics
    - If the tissue sample that was sent for molecular diagnostics is the one that was used for the diagnosis
    - Sample site
    - Site of collection
- Patient comorbidities
- Biopsy characteristics
- Genomic alterations (incl. gene rearrangements)

The drafted MTB reports, the molecular diagnostic reports (received from the LNS) and the list of patients to be discussed are shared by the INC with the moderator(s), the foreign expert as well as the LNS latest seven days prior to the MTB, to allow for preparational time into the different cases that will be discussed during the MTB.

During the MTB, discussions and conclusions around and recommendations for a patient are recorded within this same MTB report. After the MTB, these reports are shared with the participants for review – typically within one working day. After validation of its content, the signed reports are returned to the treating physician – who is ultimately responsible whether or not to follow the MTB recommendations.

The pathway can thus be summarized as follows:

1- Collect patient consent for case discussion in the RCP
2- Initial case presentation at RCP (local or national)
3- RCP endorsement of the request for MTB referral and subsequent CGP
4- Collection of patient consent prior to MTB referral and genomic testing
5- Completion of the request form by the treating physician
6- Submission of the form to both INC and LNS (pathology)
7- Genomic testing
8- Preparation of MTB report
9- Case review and discussion during the MTB, followed by treatment recommendation or enrollment in clinical study (if available)
10- Review drafted MTB report by all participants
11- Return of MTB report to treating physician

In the current organization, there is an opportunity to establish a standardized process to amongst others systematically monitor the implementation of MTB recommendations by treating physicians and to assess the associated patient outcomes. This will be further described in the subchapter 3.2.

3.2 ENVISIONED FUTURE ORGANIZATION OF MTBS

This subchapter describes the envisioned future organization of MTBs. A distinction is made between proposed improvements to the current organization of MTBs in Luxembourg, as well as proposals for more substantial improvements that will further strengthen the MTB in the future.

3.2.1 IMPROVEMENTS TO THE CURRENT ORGANIZATION

Improving the organization and impact of MTBs in Luxembourg requires a strategic shift toward more structured data sharing, systematic performance monitoring and broader national participation.

One of the most pressing needs is the standardization and interoperability of clinical and molecular data exchange across institutions. Currently, data heterogeneity and limited interoperability between the different hospital- as well as laboratory systems hinder the ability of participants of MTBs to share structured data. International standards such as HL7 FHIR, mCODE, SNOMED CT and LOINC could serve as a foundation for achieving semantic interoperability. As described in subchapter 3.1, (minimal) clinical information is manually collected and filled in on the *Request for comprehensive genomic profiling and discussion by the molecular tumor board* form. This manual process is time-consuming and prone to inconsistencies, which can affect the quality of MTB discussions. When sharing more comprehensive data with the diagnostic lab(s) (e.g., treatment history, medication history, family history, comorbidities, the performance status of a patient that may influence treatment eligibility, etc.), geneticists could take this into account when analyzing the results of the molecular testing and thus allow for tailored insights. This would enable a more nuanced interpretation of genomic alterations and thus could aid in formulating the molecular report, which in turn aids the MTB in making fully informed, evidence-based decisions.

Implementing the usage of structured data formats – with a pre-defined dataset, for example such as the OncoBox extract when available – can significantly enhance the quality and consistency of information shared prior to, as well as presented during MTB discussions. These formats allow for the integration of clinical data in a machine-readable way, facilitating both real-time decision-making and retrospective analysis. Structured data formats also support automated data validation and reduce the risk of missing or incomplete information. Moreover, it will help to limit and reduce the administrative burden on doctors and/or hospital staff, who currently must manually search through the patient's EHR to identify and transcribe the required data onto the LNS form. Automating this process through structured data exchange would not only improve efficiency, but also free up clinical resources (for patient care). To achieve this, additional support personnel will be required for the data management. In addition to supporting clinical workflows, structured datasets would also enable secondary use of data.

Equally important is the establishment of a robust framework for monitoring the MTB performance. This includes tracking key indicators such as the number of patients discussed (which is already monitored in today's organization), but additionally to track the proportion of the patients discussed for which actionable recommendations are identified, the types of recommendations made (e.g., clinical trial enrollment, off-label drug use, standard-of-care adjustments, etc.) and the rate at which these recommendations are implemented by the patient's treating physician. Furthermore, linking these data to patient outcomes – such as progression-free survival, overall survival and/or quality-of-life metrics – would provide critical insights into the real-world effectiveness of MTB-guided precision oncology. Studies have shown that such monitoring not only supports quality assurance, but also helps identify gaps in implementation and areas for improvement [15] [16].

To ensure equitable access to the MTB across the country, it is essential to increase patient enrollment from all hospitals. This can be achieved by proactively engaging with individual oncologists (and potentially other specialists involved in oncological care) in the country to understand the barriers they face in referring patients to MTBs. These barriers may include lack of awareness, perceived complexity of the referral process and/or uncertainty about the clinical utility of MTB recommendations. Tailored outreach, education and streamlined referral pathways can help address these issues. Structured interviews and/or surveys shall be conducted with oncologists and other involved HCPs to identify barriers. Targeted educational sessions shall be held to (further) demonstrate the clinical benefit of the MTB for patients. Continuous medical education programs and dedicated workshops could reinforce clinician engagement. Sharing real-world case examples where MTB recommendations directly improved patient outcomes would further build confidence. The European Society for Medical Oncology (ESMO) has emphasized the importance of clinician engagement and education in expanding access to precision oncology services [17]. A concrete example to lower a potential barrier is to add the request

form for a referral to the MTB as a downloadable document on both the LNS and INC websites, making it more accessible for specialists in the field – similar to other request forms that are currently already made available and can be downloaded from the LNS website. Another possibility is to introduce (or strengthen existing) dedicated MTB navigators in each hospital, clinical liaisons who would ensure that eligible patients are identified and referred, that data is correctly submitted and that MTB recommendations are followed-up.

Finally, improving the flow of structured data exchange between MTBs and treating physicians is crucial. This includes not only the initial data submission as described in the beginning of this subchapter, but also the return of MTB reports in a standardized, structured format that can be seamlessly integrated into the patient's EHRs. Such integration supports continuity of care and ensures that MTB recommendations are accessible and actionable at the point of care. Moreover, MTB reports should include clear summaries of recommended actions, including rationales and links to supporting evidence or clinical trials, to facilitate clinical decision-making. Linking recommendations to international guidelines and active clinical trials in Luxembourg or the Greater Region would make them more actionable. Future MTB reports should be available in both human-readable (PDF) and machine-readable (XML/JSON) formats to enable seamless integration into hospital EHRs and be made accessible through a secure data infrastructure/space.

By addressing these interconnected areas – data standardization, performance monitoring, clinician engagement and digital integration – Luxembourg can build a more cohesive, transparent and impactful MTB system that supports precision oncology at a national scale. This transformation would not only strengthen national oncology care, but also position Luxembourg as a reference hub for precision oncology. Moreover, alignment of the secure data infrastructure/space with European initiatives such as the EHDS would ensure cross-border interoperability and participation in international research networks.

3.2.2 SUBSTANTIAL IMPROVEMENTS

In addition to the improvements as proposed in subchapter 3.2.1, to further strengthen the impact and future-readiness of MTBs in Luxembourg, two more substantial key strategic enhancements are proposed.

The first substantial improvement identified and proposed is the implementation of dedicated types of testing depending on the unique clinical context, such as the introduction of Whole Genome Sequencing (WGS). Transitioning from targeted gene panels to WGS represents a transformative step in precision oncology. Unlike targeted panels that focus on a predefined set of genes, WGS provides a comprehensive view of the entire genome, enabling the detection of all classes of genomic alterations — including single nucleotide variants, structural variants, copy number changes and non-coding mutations [18] [19].

WGS offers several key advantages over panel-based testing, such as:

- **Unbiased discovery**: WGS does not rely on prior assumptions about which genes are relevant, making it particularly valuable in rare cancers, cancers of unknown primary or tumors with atypical molecular profiles [20].
- **Detection of complex genomic events**: WGS enables the identification of structural rearrangements, chromothripsis, mutational signatures and other complex events that can be missed by targeted panels [21].
- **Reusability of data**: WGS data is future-proof, as the data can be reanalyzed as new biomarkers and therapeutic targets emerge, eliminating the need for additional biopsies. This long-term utility makes WGS a powerful tool not only for immediate discussion within the MTB and clinical decision-making, but also for longitudinal patient management [20].

WGS testing can be introduced either as a replacement for the existing testing strategies, or as a complementary approach to the existing testing in selected clinical scenarios, such as e.g., for rare cancers, cancers of unknown primary or cases with no actionable findings from panel-based testing.

To ensure the successful implementation, it is essential to address the analytical demands posed by the volume and complexity of WGS data. In this context, the Luxembourgish research ecosystem — such as the Luxembourg Institute of Health (LIH), the University of Luxembourg and/or affiliated bioinformatics groups — can play a pivotal role in supporting the LNS. These institutions bring advanced computational infrastructure, bioinformatics expertise and data science capabilities that can complement LNS's diagnostic operations. This collaboration would enable the inclusion of state-of-art insights from multi-modal data, support the identification of clinically relevant patterns and enable the integration of molecular data with clinical outcomes.

As a result, for future MTBs it will be essential to broaden the range of expertise involved. In addition to oncologists, pathologists and geneticists, the input of bioinformaticians and data scientists will be increasingly important. Their contribution will focus on advanced analytical support, handling large scale genomic datasets, ensuring robust data interpretation and providing evidence-based insights to assist clinicians in decision-making. Importantly, this input complements but does not replace the clinical judgment of physicians. The ultimate responsibility for therapeutic decisions remains with the treating clinicians, who integrate these data-driven insights into the broader context of each patient's medical history, comorbidities and care preferences.

Closely related to the implementation of WGS, additional molecular data and the subsequent analytical demands is the second proposed enhancement: the integration — or strengthening — of research within the MTB framework. The rich data generated through NGS, particularly data generated through WGS, holds immense potential when combined with clinical information.

A critical enabler of this integration is the systematic linkage of genomic data with structured clinical data, such as treatment history, comorbidities and patient outcomes. This combined dataset can drive the identification of novel biomarkers and resistance mechanisms, as well as facilitate the development of machine learning models in oncology and AI-driven decision support tools [22].

Thus, to fully leverage the potential of WGS and other advanced diagnostics, research activities must be embedded directly into the MTB workflow. This ensures that genomic data is not only used for individual patient care, but also contributes to broader scientific discovery and continuous system-level learning.

To support this, Luxembourg should establish a national infrastructure for structured clinical and molecular data sharing — serving both primary (clinical) and secondary (research) purposes. Ideally, this infrastructure should be closely affiliated with, or directly embedded within the MTB and coordinated by the national cancer institute in collaboration with the hospitals, the LNS, the CFB and research institutions. This infrastructure should include:

- A secure and interoperable platform for storing and analysing WGS and clinical data
- Clear governance and ethical frameworks for data use
- Mechanisms for patient consent that support both clinical care and research

By integrating research into the MTB process, Luxembourg can not only improve care for individual patients, but also contribute to the advancement of precision oncology.

3.3 PATIENT CONSENT & DATA PSEUDONIMIZATION

In the current organization of MTBs in Luxembourg, patient data is used exclusively for direct clinical care. Consent is obtained specifically to allow the discussion of the patient's case within the MTB, ensuring that all data shared and analyzed remains within the scope of primary care. No secondary use of data — such as for research or retrospective analysis — is permitted under this framework, as a result pseudonymization is thus not applied.

Following the proposals to a future organization of MTBs as described within subchapter 3.2, the MTB would move towards a more integrated and research-enabled MTB model, for which the requirements for patient consent and data governance must evolve accordingly. In the proposed future organization, where clinical- and molecular data may be reused for research purposes, additional layers of consent will be necessary. Patients must be informed not only about the use of their data for clinical decision-making, but also about its (potential) secondary use in research, including pseudonymized data sharing across (research) institutions.

To ensure transparency and trust, patient-facing materials (e.g., consent forms, brochures, etc.) should be created to clearly explain the scope of data use, the safeguards in place and the voluntary nature of participation (for secondary use).

To support this, a robust framework for data pseudonymization, ethical oversight and tiered consent must be established. This will ensure compliance with legal and ethical standards while enabling the responsible use of data to advance precision oncology in Luxembourg.

3.3.1 CONSENT FOR PRIMARY USE OF DATA

As described in the introduction of this chapter, in its current organization, MTBs are limited to the primary use of health data – data are collected and processed solely for direct patient care. The collected and generated data are not used for secondary (e.g., research) purposes. Hence, there is currently no (need for) pseudonymization of (patient) data.

Patients must provide consent to have their cases presented and discussed in an MTB. This consent authorizes the use of personal and clinical data only for the purposes of medical decision-making within the MTB framework.

Such consent is collected by the treating physician and reflected within the patient's EHR accordingly. In case the patient does not give consent for discussion of their case within the MTB, this is also documented within the EHR (and subsequently the process stops here – no enrollment to the MTB is requested).

To improve consistency across institutions, it is recommended to develop a standardized consent template and endorse to it nationally, which will ensure a uniform language and approach to consent collection for the current MTB.

3.3.2 CONSENT FOR PRIMARY- AND SECONDARY USE OF DATA

If the data collected and processed for the MTB were to be additionally used in the future for research, registries or quality monitoring (secondary use), an additional layer of patient consent would be required. This would equally consist of a voluntary opt-in mechanism where patients need to actively agree to the (re)use of their clinical and molecular data in pseudonymized form for research purposes.

This consent for secondary use of data could be even furthered differentiated, allowing patients to choose between different levels of data sharing (e.g., use within Luxembourg only, participation in international research consortia and/or use for AI model development).

Clear explanations of pseudonymization, data protection measures in place and the right to withdraw consent at any time should be included in the consent process. Further details on how such consent form could look like can be found within subchapter 2.3 (for the usage of the DT in diabetes care respectively).

3.3.3 CONSENT MANAGEMENT

To improve efficiency and traceability, the consent collection process should be further digitalized. A practical short-term solution would be to update the oncological documentation in the patient's EHR by adding a dedicated field to capture patient consent for MTB participation (with as options: no consent, consent for primary use only or consent for both primary- and secondary use). This field could also include the functionality to attach a scanned version of a signed consent form, ensuring compliance while reflecting the hospital-specific workflow.

In the long term, consent management could be fully integrated into Luxembourg's national DSP. This would allow for harmonized, digital and auditable consent collection across all institutions, consistent with the proposals developed in the WP1 deliverables.

4. CONCLUSION

This deliverable has demonstrated how the different use cases could be functionally integrated within the current medical- and care processes.

It has shown how digital tools — such as the DT for diabetes care and the envisioned MTB for precision oncology — can enhance clinical decision-making, improve patient education and support early identification and prevention of complications.

The proposed future processes emphasize the importance of structured data exchange, interdisciplinary collaboration and research integration. They also highlight the need for robust consent management systems, data governance frameworks and technical infrastructure to support both primary- and secondary data use.

By embedding these innovations into routine care, Luxembourg can move toward a more advanced, patient-centered and research-enabled healthcare system.

The next deliverable DS4H_WP6_D6.3 will build on this foundation by describing the technical aspects on how to deploy these functional processes in a production environment.

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