Explainable Digital Twins of Patients: Towards Precision and Personalisation through Cohort Matching

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Modern healthcare services have advanced greatly due to rapid improvements in technology. The next generation of advancements requires precise and personalised treatments, especially for chronic diseases. Computational means are an effective way to achieve this through intelligent decision support assisted by superior data collection and analytics. An emerging concept to facilitate this is digital twins (DTs)—digital replicas of physical entities. DTs have evolved over the years across various industries including aerospace, control engineering, manufacturing, design optimization, and more. DTs in healthcare though, have been explored only relatively recently. One of the most interesting questions lies in creating DTs of humans to model healthcare aspects to enable intelligent decision support. Working towards this quest, this paper attempts to answer the research question: How might precise and personalised treatments for chronic diseases be planned in real-time through explainable digital twins? We attempt to answer this question in the context of breast cancer.

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1 Introduction

Digital Twins (DTs), i.e., digital replicas of physical entities, have evolved over the past several decades across various industries (Barricelli et al., 2019; Tao et al., 2018) including aerospace, control engineering, manufacturing, design optimization, and more. The parallel advancements in computation capabilities and internet connectivity that have led to 5G and beyond in telecommunication, and Industry 4.0 and beyond in industrialization, have enabled Artificial Intelligence (AI) to be coupled with DTs, thereby enhancing the capabilities and the applicability of DTs. This evolution encouraged the exploration of DTs in more human-centric sectors like healthcare as well (Katsoulakis et al., 2024).

One of the most potent questions that arose along this exploration is, "Can we create digital twins of human beings?" Why? Because they may be able to capture and help us make sense of the enormous amounts of data being generated in healthcare, and maybe this can help deliver superior healthcare through more precise and personalized medicine derived through data-driven decision support offered to clinicians and other stakeholders including patients. This thought has catalyzed several research attempts in modern times (Björnsson et al., 2020; Liu et al., 2019; Ştefănigă et al., 2024; Wickramasinghe et al., 2021; Wickramasinghe & Ulapane, 2024, 2025; Wickramasinghe, Ulapane, Andargoli, et al., 2022; Wickramasinghe et al., 2023; Wickramasinghe, Ulapane, Nguyen, et al., 2022; Wickramasinghe, Ulapane, Sloane, et al., 2024; Wickramasinghe, Ulapane, Zelcer, et al., 2024), which have attempted to conceptualize and model different aspects of humans, more specifically, patients in healthcare, and healthcare processes, with the objective of deriving data-driven intelligent decision support to help make superior clinical decisions and better manage healthcare processes.

With the involvement of all these data and AI, one of the challenges that emerges is computational complexity (Andargoli et al., 2024) which demands the likes of cloud computing (Dang et al., 2019; Liu et al., 2019). With that comes a whole lot of other questions such as privacy, security, ownership of data, intellectual property, and so on. In the pursuits towards the future, we might find solutions for such questions, but for the time being, it is fair to say that we have not yet found optimal solutions for these challenges. Therefore, whilst maintaining the hype and being ambitious, it

is also important to wind back and be practical in this pursuit for a digitally enabled healthcare.

To do this, it is still important be realistic and to think how might we make use of concepts like DTs, in a computationally feasible manner to be tractable through simple and local computers, or 'edge devices' (Rancea et al., 2024) as some call them, so that an interested healthcare provider might be able to implement locally. In the interest of this aforesaid computational simplicity, and also the added benefit of explainability, in this paper, we attempt to answer the following research question: How might precise and personalized treatments for chronic diseases be planned in real-time through explainable digital twins? We attempt to answer this question through using breast cancer as a case study for a chronic disease. More specifically, we target at achieving more precision and personalization in planning a kind of immunotherapy for Triple-Negative Breast Cancer (TNBC) (Foulkes et al., 2010).

2 Review of Related Literature

2.1 Digital Twins (DTs) in Healthcare

A recent scoping review in 2024 by (Katsoulakis et al., 2024) has identified eight main applications of DTs for health; namely, personalized medicine, clinical trials, biomarker and drug discovery, bio-manufacturing, device design, surgical planning, hospital management design & care coordination, and wellness. Several years before, in 2021, (Wickramasinghe et al., 2021) too identified similar applications for DTs in healthcare and viewed DTs as mathematical models irrespective of the application. (Wickramasinghe et al., 2021) identified DTs to function as grey box, surrogate, or black box mathematical models. Grey box DTs are partially or fully governed by well-known principles, such as physics, or statistics. Surrogate DTs need not necessarily have underlain sophisticated analytics capabilities but can be useful for display purposes—such as a dashboard display of an emergency department workflow. Black box digital twins are often underpinned by sophisticated machine learning models, such as neural networks. They may not be apparently explainable but usually have strong data handling and analytics utility. Building on this knowledge, in this paper as an attempt to answer our target research question, we attempt to combine the grey box and surrogate model attributes to realize DTs targeted at personalized medicine. Our choice of grey box and surrogate attributes

helps our DTs function in real-time on edge devices while being computationally simple and explainable.

2.2 Immunotherapy for Triple-Negative Breast Cancer (TNBC)

TNBC is an aggressive type of breast cancer. It is linked with the lack of three receptors: namely, estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2) (Dass et al., 2021; Foulkes et al., 2010). As a result, TNBC is typically more aggressive. It is also faster in growth rate and has higher risk of metastasis. Moreover, it has limited treatment options and poor prognosis (Kesireddy et al., 2024; Obidiro et al., 2023).

In this backdrop, certain immunotherapies, such as certain immune checkpoint inhibitors have been identified as potential treatment options for TNBC. Such immune checkpoint inhibitors typically make cancer cells more vulnerable to our body's own immune system, thereby making our own immune system work against cancer. However, when such treatment is carried out, it is not only the cancer cells that become vulnerable to the immune system, because such immunotherapies typically cannot be delivered locally. When delivered, such treatments affect the whole body, and thus healthy cells too become more vulnerable to the immune system, leading to certain complications and side-effects. That is a trade-off of this type of treatment. However, immune checkpoint inhibitors such as PD-1 and PD-L1 inhibitors have been approved in certain countries, including Australia, as a form of immunotherapy less than a decade ago to treat TNBC. The outcomes and side effects, though, have remained variable. It is therefore beneficial if it is possible to predict likely prognosis prior to treatment, hence we have chosen TNBC as a case study for our DTs. Through this case study we explore as to how DTs might be used for precise and personalized planning of PD-1/PD-L1 inhibitor treatment for TNBC candidates by trying to find beforehand, who is statistically congruent to best respond to which PD-1/PD-L1 inhibitor treatments.

3 Methodology

We used an approach inspired by Design Science Research Methodology (DSRM) (Hevner et al., 2010) to design a DT platform to help precise and personalized planning of PD-1/PD-L1 inhibitor treatments for TNBC. The approach followed

is depicted in Figure 1. Details about each step are provided in the following subsections.

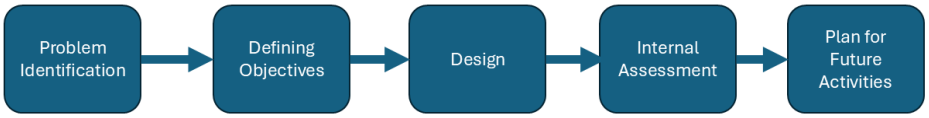

Figure 1: The DSRM-inspired methodology followed in this study

3.1 Problem Identification Phase

This work started through a collaboration between the authors and a team of cancer biologists who study the effects of immunotherapies on breast cancer at a cellular biomarker level. This collaboration started in a backdrop of immune checkpoint inhibitor treatments such as PD-1 and PD-L1 inhibitors have been approved in Australia recently, especially for TNBC patients. The state of matters was that such treatments were quite expensive, and a limited number of candidates were eligible to receive them in Australia. Even among the limited recipients, the outcomes and the side effects were variable. Therefore, we asked the pertinent question as to whether we can predict the prognosis of PD-1 and PD-L1 inhibitor treatments on TNBC patients, as this would enable the identification of best receptive patients, prior to receiving immunotherapy treatment, and in turn this would reduce the incidences of adverse outcomes and side-effects. This line of thought led the authors, and the collaborators to secure the Victorian Medical Research Acceleration Fund (VMRAF) grant GA-F4669635-1352, to explore avenues for predicting prognosis of PD-1 and PD-L1 inhibitor treatments, making use of genetic information obtained from TNBC patients. The view from the collaborating cancer biologists was that they have a wealth of genetic information, but it was difficult to find direct patterns. This opened the avenue to explore the use of machine learning and AI to address this problem.

Moreover, as part of the 'problem identification' phase, a rapid review of literature was conducted with the objective of mapping out the diversity of immunotherapy treatment options and outcomes pertaining to TNBC. The protocol followed for this review was published in Open Science Framework at: https://osf.io/2bzds/.

The PRISMA guidelines (Stevens et al., 2018) and the Cochrane methodology (Garritty et al., 2024) were followed for reviewing the literature and reporting. The outcome of this review was a set of themes that summarized the diversity of immunotherapy treatment options for TNBC, along with associated outcome measures and side-effects. These findings are summarized in Figure 2 in the Results section.

3.2 Defining Objectives Phase

Following the 'problem identification' phase, we defined objectives for a potential solution. Given the nascency of this area, we decided to be guided by the themes identified from the conducted rapid review to design a computationally simple web-based DT platform that can provide clinical decision support on precise and personalized planning of PD-1/PD-L1 treatments for TNBC. The web-based function was chosen to ensure easy accessibility over the internet, while computational simplicity was weighed in to ensure ability to implement on edge devices and local servers. To achieve computational simplicity, for this design we chose offering decision support purely based on statistical congruence—meaning assessing how statistically similar a present patient is to cohorts of past patients. Thereby we derive decision support based on DTs constructed from a cohort matching approach.

3.3 Design Phase

At the design phase we planned three key aspects for a solution. The first was the patient journey with the DT platform integrated within. The planned patient journey is depicted in Figure 3 in the Results section. This DT platform was planned to perform as a clinical decision support tool. Therefore, it is designed primarily for the use of clinicians. However, it can be used by clinicians in consultation with patients for shared decision-making. The second aspect we designed was a web-based frontend to display results that would assist clinical and shared decision-making. The designed web-based frontend is depicted in Figure 4 in the Results section. Thirdly, we designed graphical means to display results more elaborately along with DTs of patients identified based on statistical congruence, or cohort matching—meaning, finding cohorts of past patients that statistically best match a present patient. Details about the functionality of the DT dashboard are provided in the Results section.

3.4 Internal Assessment Phase

Following the 'design phase,' the designs were informally discussed with the collaborating cancer biologists. Their feedback, thoughts and recommendations were recorded. Their recommendations are summarized in the Results section.

3.5 Plan for Future Work

As future work it was planned to refine the web-based frontend as well as the statistical rules for cohort matching based on the feedback received from the cancer biologists and implement the platform. Initially, due to the lack of data from TNBC patients, it was decided to run the platform based on synthetic data produced mimicking real-world patients.

4 Results and Discussion

4.1 Diversity of Immunotherapy Treamtments on TNBC

The findings from the rapid review that was conducted as part of the 'problem identification' phase were summarized highlighting the diversity of immunotherapy treatment options for TNBC, along with associated outcome measures and side-effects. These findings are presented in Figure 2.

4.2 The Planned Patient Journey

The patient journey that was planned as part of the 'design phase' is depicted in Figure 3. The DT platform is integrated within the patient journey as a clinical decision support tool plus a decision aid for shared decision making through the collaboration of both clinicians and patients.

4.3 The Desiged Web-Based DT Frontend

The designed web-based DT frontend is depicted in Figure 4 and it is followed by a description about how decision support is derived through our proposed cohort matching approach.

Immunotherapy Type	Treatment Drug	Objective response rate (ORR) (%)	Median Problem free survival (PFS) Range (months)	Median Overall survival (OS) Range (months)	Specific Biomarkers	Significant Findings	Adverse Events / Safety
PD-1 Inhibitors	Pembrolizumab	21 - 43%	1.8 - 11.7	6.3 - 26.0	PD-L1 CPS ≥1, TMB, CD8+ T-cells	PD-L1 CPS ≥1 correlated with improved responses and survival.	Fatigue, nausea, diarrhea; immune-related AEs (e.g., rash, thyroid dysfunction).
	Nivolumab	12.5 - 20%	1.4 - 3.7	5.6 - 8.1	PD-L1+, TILs, sTILs, immune gene expression	Modest responses; higher benefit in biomarker-selected populations (e.g., TILs).	Fatigue, anaemia, immune-related toxicities (e.g., colitis, pneumonitis).
	Camrelizumab	43.3 - 81.3%	3.7 - 13.6	8.1 - 12	CD8+ T-cells, PD-L1+, IL-8, VEGFR2 expression	Continuous dosing improved outcomes; biomarkers CD8+ T-cells showed influence.	Anaemia, neutropenia, fatigue; increased toxicity with continuous dosing.
	Toripalimab	66%	8.4	32.8 (PD-L1+)	ctDNA, PD-L1+	High responses observed in PD-L1+ subgroups; ctDNA detection associated with relapse.	Immune-related AEs consistent with PD-1 inhibitors (e.g., rash, thyroid dysfunction).
	SHR-1210	No data	3.7	Not reported	TGF-β, OPN, PD-1/PD-L1 expression	Combination with low-dose Apatinib improved outcomes; biomarkers influenced response.	Manageable safety; mild side effects, dose reductions minimized severe toxicities.
PD-L1 Inhibitors	Atezolizumab	20 - 56%	4.3 - 7.5	14.7 - 25.0	PD-L1+, CD8+ T-cells, TILs	PD-L1+ tumours benefited most; strong association with CD8+ T-cells.	Fatigue, neutropenia, nausea; immune-related AEs (e.g., hypothyroidism, colitis).
	Durvalumab	36 - 53.4%	2.7 - 6.1	18.3 - 21.2	BRCA mutations, PD-L1+, TILs	Survival benefits observed in early-stage and combination therapies.	Nausea, anaemia, fatigue; immune-related AEs observed, including macrophage responses.
	Avelumab	18.2 - 34.8%	3.6 - 5.3	Limited data	BRCA mutations, DNA damage repair	Durable responses in DNA damage repair-positive tumours and BRCA-altered cancers.	Haematological toxicities (e.g., anaemia, neutropenia, thrombocytopenia).
	Adebrelimab	90% (pCR)	No data	No data	PD-L1+	High pCR rates with combination therapy; manageable safety profile.	Grade 3-4 AEs common (e.g., neutropenia, anaemia, leukopenia); manageable overall profile.
PD-1 + VEGFR Inhibitors	Apatinib, Famitinib	43.3 - 81.3% (continuous dosing)	3.7 - 13.6	8.1 - 12	CD8+ T-cells, PD-L1+, IL-8, VEGFR2 expression	Continuous dosing improved outcomes; biomarkers like CD8+ T-cells showed influence.	Haematological toxicities (anaemia, neutropenia); hand-foot syndrome; hypertension.
PD-1/PD-L1 + PARP Inhibitors	Olaparib, Talazoparib, Fuzuloparib	6.9 - 34.8%	3.7 - 6.1	Limited data	BRCA mutations, PD-L1+, DNA damage response	Biomarkers such as BRCA mutations and PD-L1 trends influenced efficacy.	Haematological toxicities (e.g., anaemia, neutropenia), fatigue, hypertension.
Radiotherapy + Immunotherapy	Various PD-1/PD-L1 inhibitors	17.6 - 90%	No data	No data	PD-L1+, TMB, CD8+ T-cells	Enhanced pathological complete response (pCR) rates and objective response rates.	Lymphopenia, dermatitis, fatigue; immune-related AEs observed with combination therapy.
Combination with Chemotherapy	Nab-paclitaxel, Paclitaxel, Carboplatin, Epirubicin, Capecitabaline, Eribulin	29 - 91.3%	4.2 - 13.6	16.1 - 25.9	PD-L1 CPS ≥1, TILs, CD8+ T-cells	Combination therapies consistently outperformed monotherapy, particularly in PD-L1+.	Neutropenia, anaemia, nausea; immune-related AEs with PD-1/PD-L1 inhibitors.

Figure 2: Key findings from the rapid review (https://osf.io/2bzds/) conducted on immunotherapy for TNBC

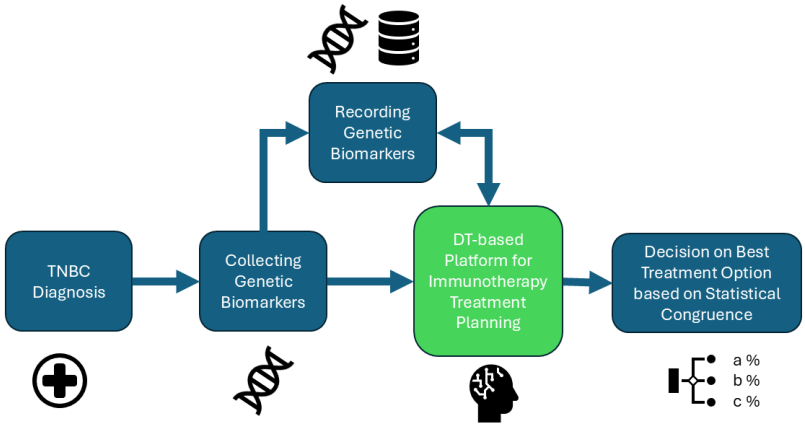

Figure 3: Proposed patient journey with DT platform integrated

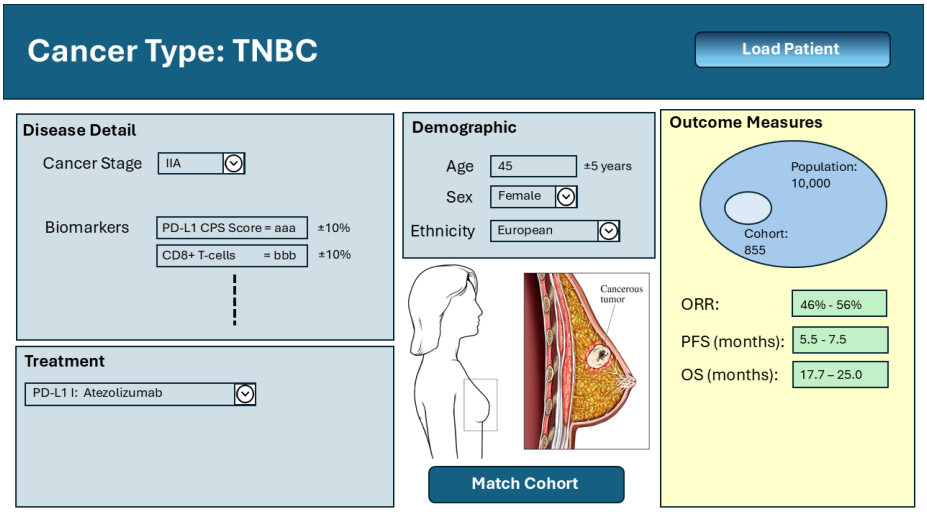

Figure 4: Snapshot of the proposed DT frontend dashboard for precise and personalized immunotherapy treatment planning for TNBC (please zoom in if required to read texts in this image)

The DT frontend in Figure 4 will be accessible for clinicians as a clinical decision support tool. It can be used in collaboration with patients for shared decision making. At the top right, it has a button named 'Load Patient.' That is where the process starts. When a patient is in front of the clinician, the process can be started by the clinician pressing on the 'Load Patient' button. This will provide an option

like scanning a unique QR code for the patient. Once the unique identifier (QR code or similar) is scanned, the patient's genetic biomarkers along with other relevant information will be fetched from a dedicated server. The fetched information will be displayed onscreen as shown in Figure 4. To confirm the fetched data matches the present patient, a preceding popup window will appear, showing some patient personal identifiers like name and date of birth. That information will appear only on that popup window but not on the DT screen shown in Figure 4 to preserve patient's privacy. This popup window can be cross-checked by the clinician and the patient to confirm the right information has been fetched. Once confirmed, the popup window can be closed, and then the relevant information will appear on the DT screen shown in Figure 4.

As can be seen in Figure 4, patient information is stratified into two groups, i.e., demographic information and disease detail. Demographic information includes patient's age (in years, inclusive of a range plus or minus five years for cohort matching), sex (Male or Female), and ethnicity (e.g., African, East Asian, South Asian, Southeast Asian, Middle Eastern and North African (MENA), European, Hispanic or Latino, Indigenous Peoples, Pacific Islander, Mixed or Multi-Ethnic, etc.). All such demographic details are eventually used to select a cohort of past patients to which the present patient will match on a statistically congruent basis—thereby achieving a degree of personalization.

Then, as disease details, the dashboard is specifically designed for TNBC. The other main disease information considered is the cancer stage (e.g., Stage IA, IB, IIA, etc.). Next, relevant genetic biomarkers are considered. In the context of TNBC and PD-1/PD-L1 inhibitors, the literature review we conducted as part of the 'problem identification' phase revealed that biomarkers such as PD-L1 CPS score, CD8+ T-cell infiltration and Tumor Mutational Burden amongst others are relevant. These biomarkers are designed to be considered as quantitative values, i.e., a real-valued number. For cohort matching, these numbers are considered with a margin of $\pm$10%. That means, past patients who have had biomarker values within $\pm$10% of the present patient will form a matching cohort to the present patient.

Next, the clinician can select available immunotherapy treatment options (e.g., PD-1 inhibitors (e.g., Pembrolizumab, Nivolumab, Camrelizumab, Toripalimab, or SHR-1210), PD-L1 inhibitors (e.g., Atezolizumab, Durvalumab, Avelumab, or

Adebrelimab), and click on the button named 'Match Cohort.' This will then fetch the outcome data of the past patients within the matching cohort to the present patient, and display certain outcome measures, and possibly side-effects also as shown in the 'Outcome Measures' panel in Figure 4. Displayed outcome measures include the likes of Objective Response Rate (ORR), Problem Free Survival (PFS) range in months, and Overall Survival (OS) range in months, and likely side-effects (e.g., fatigue, nausea, list of immune-related adverse events (AEs), etc.). This display can be used by clinicians to make informed decisions about the best treatment options that are statistically congruent pertaining to the present patient, thereby achieving a degree of personalization. These decisions can be made collectively with patients, thereby achieving patient empowerment through shared decision making. When presenting outcome measures, data of a present patient is interfaced and used in an intelligent digital model of a patient constructed for the purpose of clinical decision support, thereby the DT paradigm being realized. Furthermore, we have planned more elaborate displays of outcome measures such as the one in Figure 5, which illustrates the population of past patients along with a discovered DT (i.e., the most statistically congruent cohort to the present patient). Such displays can better express the degree of personalization that has taken place.

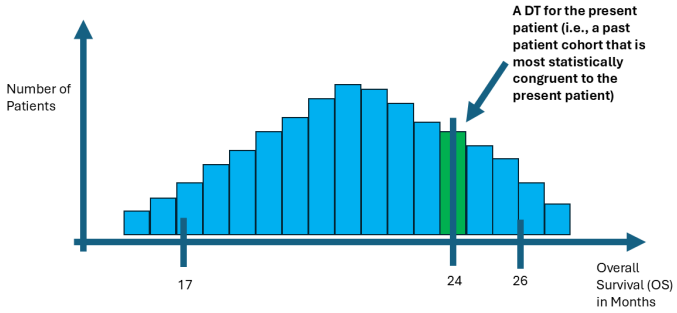

Figure 5: Population of past patients alongside a discovered DT (i.e., the most statistically congruent cohort to the present patient) depicting personalization of outcome measures

4.4 Outcomes from the Internal Assessment Phase

From the discussions that were carried out with the collaborating caner biologists, their main suggestion was about the biomarkers. They suggested using biomarker quantities normalized per square area and normalized per number of cancer cells

present. In an intuitive mathematical sense, normalizing biomarkers as such makes great sense, and therefore we decided to use normalized values in our future implementations of this platform.

5 Conclusions

Answering the research question "How might precise and personalized treatments for chronic diseases be planned in real-time through explainable digital twins?" was attempted. A DSRM-inspired approach was followed to answer the research question. A computationally simple, real-time, and explainable DT platform that is based on statistical congruence was proposed. This is designed to provide clinical decision support to achieve precise and personalized planning of immunotherapy treatments for TNBC.

This paper contributed to theory by proposing an approach of matching cohorts of past patients based in statistical congruence to present patients as a form DTs capable of deriving decision support and insights based on statistics, thereby preserving computational simplicity, explainability and the ability to implement on edge devices and local servers to offer real-time clinical decision support.

As a contribution to practice, this paper proposed a DT-incorporated patient journey, frontend designs for a DT platform, and certain statistical and logical steps for deriving DTs and insights through cohort matching in a computationally simple and explainable manner.

TNBC and immunotherapy, the target healthcare context of this work, is new and we are restricted by the lack of data from TNBC patients. Therefore, we had to resort to proceeding with synthetic data to develop our algorithms. The lack of real data and having to rely on synthetic data is a limitation that underpins our work.

DTs in healthcare are at their infancy but there is the potential for significant benefits to realize simultaneously more personalized and precise clinical decision support. Future work will fucus on refining our algorithms and DT platforms based on feedback received from our collaborating cancer biologists and the latest findings in cancer treatment, all whilst being condescended to value-based healthcare principles.

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References

Andargoli, A. E., Ulapane, N., Nguyen, T. A., Shuakat, N., Zelcer, J., & Wickramasinghe, N. (2024). Intelligent decision support systems for dementia care: A scoping review. *Artificial Intelligence in Medicine*, 102815.

Barricelli, B. R., Casiraghi, E., & Fogli, D. (2019). A survey on digital twin: Definitions, characteristics, applications, and design implications. *IEEE access*, *7*, 167653-167671.

Björnsson, B., Borrebaeck, C., Elander, N., Gasslander, T., Gawel, D. R., Gustafsson, M., Jörnsten, R., Lee, E. J., Li, X., & Lilja, S. (2020). Digital twins to personalize medicine. *Genome medicine*, *12*, 1-4.

Dang, L. M., Piran, M. J., Han, D., Min, K., & Moon, H. (2019). A survey on internet of things and cloud computing for healthcare. *Electronics*, *8*(7), 768.

Dass, S. A., Tan, K. L., Selva Rajan, R., Mokhtar, N. F., Mohd Adzmi, E. R., Wan Abdul Rahman, W. F., Tengku Din, T. A. D. A.-A., & Balakrishnan, V. (2021). Triple negative breast cancer: a review of present and future diagnostic modalities. *Medicina*, *57*(1), 62.

Foulkes, W. D., Smith, I. E., & Reis-Filho, J. S. (2010). Triple-negative breast cancer. *New England journal of medicine*, *363*(20), 1938-1948.

Garritty, C., Hamel, C., Trivella, M., Gartlehner, G., Nussbaumer-Streit, B., Devane, D., Kamel, C., Griebler, U., & King, V. J. (2024). Updated recommendations for the Cochrane rapid review methods guidance for rapid reviews of effectiveness. *bmj*, *384*.

Hevner, A., Chatterjee, S., Hevner, A., & Chatterjee, S. (2010). Design science research in information systems. *Design research in information systems: theory and practice*, 9-22.

Katsoulakis, E., Wang, Q., Wu, H., Shahriyari, L., Fletcher, R., Liu, J., Achenie, L., Liu, H., Jackson, P., & Xiao, Y. (2024). Digital twins for health: a scoping review. *NPJ digital medicine*, *7*(1), 77.

Kesireddy, M., Elsayed, L., Shostrom, V. K., Agarwal, P., Asif, S., Yellala, A., & Krishnamurthy, J. (2024). Overall survival and prognostic factors in metastatic triple-negative breast cancer: a national cancer database analysis. *Cancers*, *16*(10), 1791.

Liu, Y., Zhang, L., Yang, Y., Zhou, L., Ren, L., Wang, F., Liu, R., Pang, Z., & Deen, M. J. (2019). A novel cloud-based framework for the elderly healthcare services using digital twin. *IEEE access*, *7*, 49088-49101.

Obidiro, O., Battogtokh, G., & Akala, E. O. (2023). Triple negative breast cancer treatment options and limitations: future outlook. *Pharmaceutics*, *15*(7), 1796.

Rancea, A., Anghel, I., & Cioara, T. (2024). Edge computing in healthcare: Innovations, opportunities, and challenges. *Future internet*, *16*(9), 329.

Ştefănigă, S. A., Cordoş, A. A., Ivascu, T., Feier, C. V. I., Muntean, C., Stupinean, C. V., Călinici, T., Aluaş, M., & Bolboacă, S. D. (2024). Advancing Precision Oncology with Digital and Virtual Twins: A Scoping Review. *Cancers*, *16*(22), 3817.

Stevens, A., Garritty, C., Hersi, M., & Moher, D. (2018). Developing PRISMA-RR, a reporting guideline for rapid reviews of primary studies (Protocol). *Equator Network*, 1-12.

Tao, F., Zhang, H., Liu, A., & Nee, A. Y. (2018). Digital twin in industry: State-of-the-art. *IEEE Transactions on industrial informatics*, *15*(4), 2405-2415.

Wickramasinghe, N., Jayaraman, P. P., Forkan, A. R. M., Ulapane, N., Kaul, R., Vaughan, S., & Zelcer, J. (2021). A vision for leveraging the concept of digital twins to support the provision of personalized cancer care. *IEEE Internet Computing*, *26*(5), 17-24.

Wickramasinghe, N., & Ulapane, N. (2024). Digital Twins of Patients: A Liquid Neural Network Interpretation. *ACIS 2024 Proceedings. 32. https://aisel.aisnet.org/acis2024/32.* https://aisel.aisnet.org/acis2024/32

Wickramasinghe, N., & Ulapane, N. (2025). A Solution for the Health Data Sharing Dilemma: Data-Less and Identity-Less Model Sharing Through Federated Learning and Digital Twin-Assisted Clinical Decision Making. *Electronics*, *14*(4), 682.

Wickramasinghe, N., Ulapane, N., Andargoli, A., Ossai, C., Shuakat, N., Nguyen, T., & Zelcer, J. (2022). Digital twins to enable better precision and personalized dementia care. *JAMIA open*, *5*(3), ooac072.

Wickramasinghe, N., Ulapane, N., Andargoli, A., Shuakat, N., Nguyen, T., Zelcer, J., & Vaughan, S. (2023). Digital twin of patient in clinical workflow. *Proceedings of the Royal Society of Victoria*, *135*(2), 72-80.

Wickramasinghe, N., Ulapane, N., Nguyen, T. A., Andargoli, A., Ossai, C., Shuakat, N., & Zelcer, J. (2022). Towards discovering digital twins of dementia patients: matching the phases of cognitive decline. *Alzheimer's & Dementia*, *18*, e066336.

Wickramasinghe, N., Ulapane, N., Sloane, E. B., & Gehlot, V. (2024). Digital Twins for More Precise and Personalized Treatment. In *MEDINFO 2023—The Future Is Accessible* (pp. 229-233). IOS Press.

Wickramasinghe, N., Ulapane, N., Zelcer, J., & Saffery, R. (2024). 'Omics-Based Digital Twins for Personalised Paediatric Healthcare. *Studies in Health Technology and Informatics*, *318*, 180-181.