



# Non-Imaging Medical Data Synthesis for Trustworthy AI: A Comprehensive Survey

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Data quality is a key factor in the development of trustworthy AI in healthcare. A large volume of curated datasets with controlled confounding factors can improve the accuracy, robustness, and privacy of downstream AI algorithms. However, access to high-quality datasets is limited by the technical difficulties of data acquisition, and large-scale sharing of healthcare data is hindered by strict ethical restrictions. Data synthesis algorithms, which generate data with distributions similar to real clinical data, can serve as a potential solution to address the scarcity of good quality data during the development of trustworthy AI. However, state-of-the-art data synthesis algorithms, especially deep learning algorithms, focus more on imaging data while neglecting the synthesis of non-imaging healthcare data, including clinical measurements, medical signals and waveforms, and electronic healthcare records (EHRs). Therefore, in this paper, we will review synthesis algorithms, particularly for non-imaging medical data, with the aim of providing trustworthy AI in this domain. This tutorial-style review paper will provide comprehensive descriptions of non-imaging medical data synthesis, covering aspects such as algorithms, evaluations, limitations, and future research directions.

CCS Concepts: • **Computing methodologies** → **Modeling methodologies**.

Additional Key Words and Phrases: medical data synthesis, Electronic Healthcare Records

## 1 INTRODUCTION

The use of Artificial Intelligence (AI) on health data is creating promising tools to assist clinicians in fields such as automatic evaluation of diseases and prognosis management [61]. However, AI algorithms can be biased, unfair, or unethical, with a high risk of privacy breaches [151]. These AI algorithms, failing to win human trust [79], hinder the development and large-scale applications of AI in healthcare scenarios. Over the past few decades, researchers have been working on developing *trustworthy AI* [71, 151] by improving robustness, variety, and transparency throughout the AI lifecycle, where the training data of AI algorithms [71] is identified as a key factor in achieving trustworthy AI.

A trustworthy training dataset should have a set of (overlapping) properties: 1) a large quantity; 2) an unbiased variety; 3) strict ethical regulations during collection [102, 145]; and 4) a low risk of privacy breaches. Considering

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the complex procedure and strict protocols of medical data acquisition, practitioners face enormous difficulty acquiring a large quantity of high-quality medical data in the real world. In addition to the challenges of data acquisition, healthcare data is sensitive, and sharing or working with it can easily lead to a violation of patients' privacy.

To address these problems, researchers have developed data synthesis algorithms. By synthesizing medical data instead of acquiring it from the real world, they can improve the size and variety of training datasets, impute missing values, and protect patients' privacy. These synthetic data can serve as a qualified training set for trustworthy AI algorithms [83, 99]. Conventional data synthesis algorithms are based on sampling, where data is generated by sampling from the data distribution after modeling it. However, this statistical sampling requires prior knowledge of the distributional functions. Recently, deep learning models have been developed for data synthesis, as they do not require an explicit selection of distributional functions, and their performance has been widely validated, especially on medical images [49, 98]. These algorithms can generate various types of synthetic medical data, which can be used in various AI algorithms [161].

Synthetic medical data has two forms: imaging data and non-imaging data. While medical imaging data, such as X-ray, CT, and MR images, are important for lesion observation and quantification, they cannot be relied on solely for diagnosis and prognosis. Therefore, analyses of non-imaging medical data are crucial in large-scale *in silico* clinical trials. However, despite the importance of both imaging and non-imaging data, we have observed that non-imaging data has received little attention in data synthesis algorithms and computer-aided medical applications in recent decades. Furthermore, we have found that the development of synthesis algorithms has been dominated by deep learning models, and there has been a lack of detailed explanations on non-deep learning methods and their relationships in the literature.

To bridge the research gaps and provide guidance on trustworthy AI-based non-imaging medical data synthesis, this paper presents a comprehensive survey of algorithms, evaluation metrics, and related datasets. During our literature review, we identified seven papers focusing specifically on non-imaging medical data synthesis algorithms (Table 1). While some empirical studies [45, 149, 159] conducted comparative analyses of EHR synthesis using different algorithms, their scope was limited and did not provide a comprehensive comparison of all algorithms and evaluation methods. Review papers such as [47, 54] only focused on specific aspects of data synthesis algorithms and did not cover the entire workflow of non-imaging medical data synthesis. Although comprehensive reviews like [55, 96] provided literature reviews of non-imaging data synthesis algorithms, they too lacked a comprehensive dataset review and did not consider the trustworthy aspects of data synthesis algorithms. Furthermore, these comprehensive reviews mainly listed the algorithms without providing proper explanations or discussing their relationships with one another.

In contrast, our review aims to provide a more comprehensive and up-to-date survey of non-imaging medical data synthesis algorithms, covering a broader range of synthesis techniques, evaluation metrics and open-sourced datasets that contribute to the development of trustworthy AI. We also include a detailed description of the mathematical and statistical foundation of non-imaging data synthesis and provide a tutorial for non-imaging synthesis algorithms. Moreover, we address the limitations and research issues related to non-imaging medical data synthesis and provide guidance for data synthesis algorithms that contribute to trustworthy AI. This survey offers three contributions:

- Providing a comprehensive and up-to-date survey on non-imaging medical data synthesis algorithms;
- Clearly defining and describing non-imaging medical data, including open-source datasets and pre-processing methods;
- Explaining the mathematical and statistical principles behind non-imaging data synthesis and providing a step-by-step guide to non-imaging synthesis algorithms.

Table 1. Comparison of existing non-imaging data review studies. \*In [45], the term "data utility" was used to refer to data fidelity metrics, which could be confusing. \*\* The paper only included a review on fully synthetic datasets.

Paper title	Number of studies	Period	Dataset review	Evaluation metrics	Contents
[149]	2	~2021	no	Fidelity and privacy	Empirical study
[45]	8	~2020	no	Fidelity* and privacy	Empirical study
[55]	34	~2022	no	Fidelity, utility and privacy	Comprehensive review paper
[47]	72	~2022	yes**	NaN	Review paper focusing on applications and use cases
[96]	70	~2022	no	Fidelity, utility and privacy	Comprehensive review paper
[54]	NA	~2022	no	Fidelity, utility and privacy	Review paper focusing on evaluation metrics
[159]	NA	~2022	no	Fidelity, utility and privacy	Empirical study
Ours	82	~2023	yes	Fidelity, utility, privacy and fairness	Comprehensive review paper

The remainder of this review paper is structured as follows: Section 2 outlines the criteria used to collect and filter the literature reviewed in this survey, and presents the taxonomy used to systematically and coherently organize it. In Sections 3, 4, and 5, we will introduce three major types of data generation algorithms. In Section 6, we will discuss three critical aspects of trustworthy synthetic data quality and their corresponding measurements. In Section 7, we will present several datasets categorized by their data types, and provide commonly practiced pre-processing procedures for these data types. Finally, in Section 8, we will analyze the limitations of non-imaging medical data synthesis and propose potential research directions for non-imaging data synthesis that consider trustworthy AI.

## 2 LITERATURE COLLECTION AND TAXONOMY

All papers included in this review were obtained by a three-stage searching strategy.

First, we selected the papers regarding non-imaging healthcare data synthesis from January 1st, 2000 to July 1st, 2022 with the keywords "data synthesis", "synthetic data", "data generation", "data augmentation", and "oversampling". They were concatenated in an "or" logic relation. We confined our search to computer sciences area and deleted the papers that are not related according to their abstracts. We focus on two types of non-imaging medical data during our searching process: tabular data and sequential data. Other non-imaging data medical types, although provide crucial information in healthcare analysis, are not discussed. It is because 1) the synthesis and applications of these data types are scarce, i.e., social networks for infectious [8] or family inherited diseases; or 2) the synthetic data does not provide new information for downstream tasks, e.g., medical reports [62]. At this stage, we used Scopus (<https://www.scopus.com>) as our search engine because it is the largest database for peer-reviewed literature. After the first screening, 988 papers were selected.

During the initial stage of our reference search, we did not specifically focus on healthcare data synthesis algorithms. For instance, we included SMOTE [20], which proposes an algorithm from an application-agnostic perspective, without identifying any specific use cases. Therefore, after the preliminary screening based on

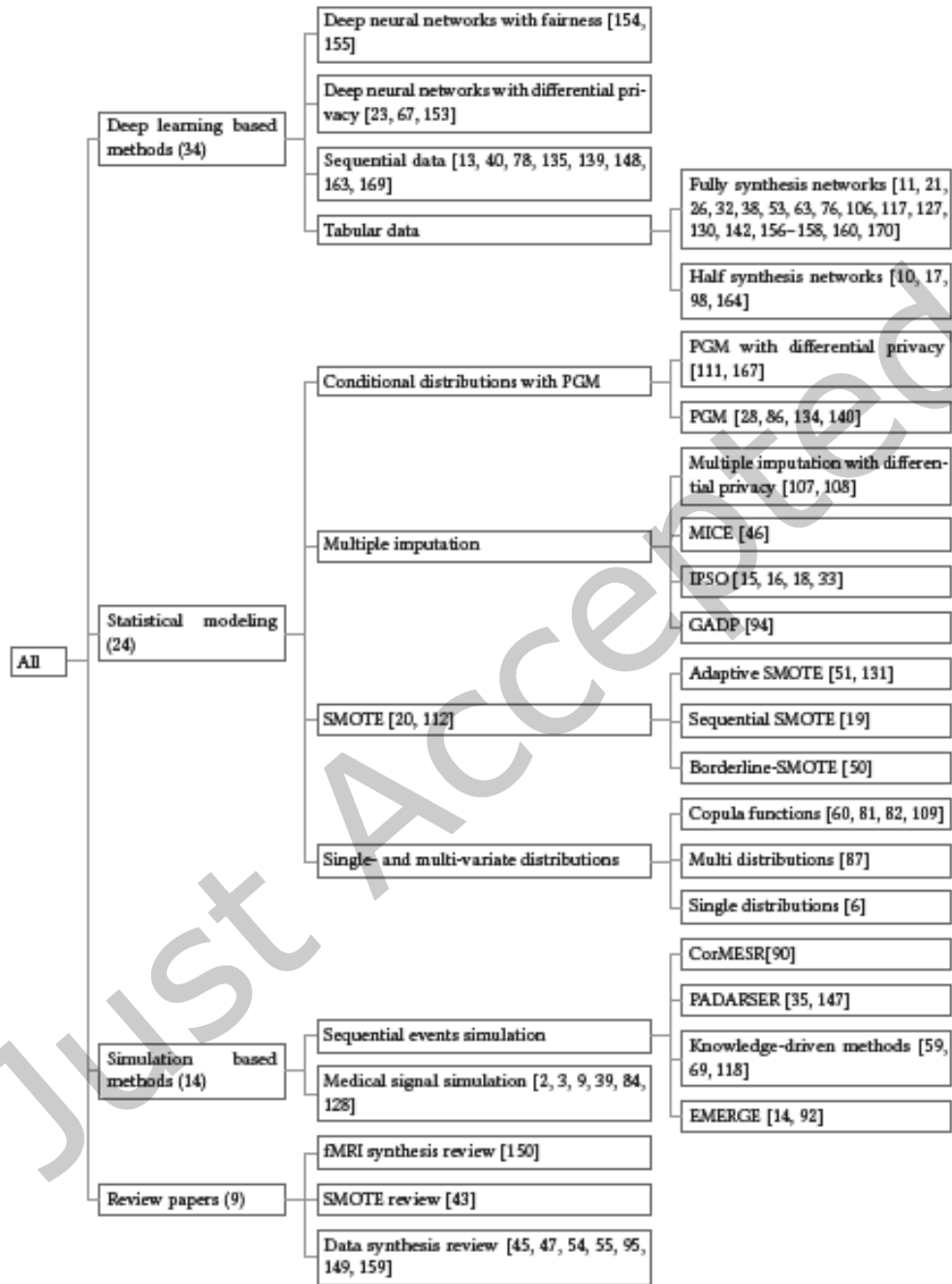


Fig. 1. All papers included in this review. These papers are categorized by their synthesis algorithms.

abstracts, we read the papers more thoroughly and eliminated those that were not healthcare-related or did not propose innovative algorithms. This left us with a total of 67 papers.

In the final stage of our literature collection process, we thoroughly read the selected papers and summarized their methods and applications. Additionally, we checked the reference lists of these papers to ensure we had not missed any relevant literature. We did not include papers from *Arxiv* (<https://arxiv.org/>) in the first two stages as they are not peer-reviewed. However, highly-cited *Arxiv* papers (with a citation count >20) were included in the reference stage. After the final stage, we selected and analyzed 82 papers, as shown in Figure 1.

### 3 SIMULATION-BASED ALGORITHMS

In this section, we will introduce simulation-based algorithms for data synthesis. Simulation-based methods aim to generate synthetic data by simulating underlying real-world mechanisms. We have identified two categories of simulation-based algorithms based on their target non-imaging data types.

#### 3.1 Medical signal simulation

Simulation-based algorithms have been widely used, particularly for generating medical signals, such as MEG, EEG, and fMRI [150]. For medical signal simulation, simulation-based methods use the summation of three basic components of the signals: a baseline signal, a signal of interest (in fMRI simulation, this signal of interest is the BOLD signal; in EEG simulation, the signal of interest is the electrical signals produced by the brain.) and noises, and the final simulated signals are the summation of these three basic components.

The baseline signal in simulated signals represents their basic numerical level, and the baseline values can be tissue-specific [39]. However, some algorithms simply set the baseline value to zero [3]. For the synthesis of signals of interest, most medical signal methods consider the correlations among signals from different brain regions. Multivariate autoregressive modeling (MAR) [9, 128] provides spatial-related correlations for medical signal simulation. The noises can be modeled by Gaussian distributions or mixture Gaussian distributions [84]. Motion noise can also be added to simulate patient motion during scanning.

#### 3.2 EHR simulation

One of the most well-known simulation-based synthesis algorithms for EHR is the Synthetic Electronic Medical Records Generator (EMERGE) project [14, 93]. This project synthesizes time series of events, which are referred to as "patient care models", "care flow", or "caremaps", for both general populations and populations with specific diseases. Patient care models consist of a series of care-related tasks involved in managing a patient trajectory and provide a workflow guidance for patients with specific diseases [48].

EMERGE began by synthesizing a group of basic demographic information and symptoms reported during the first visits. Then a series of timestamps for each synthetic patient were synthesized. For each timestamp of each synthetic patient, EMERGE selected the closest healthcare record from the real dataset based on weighted Euclidean and Jaccard distances. Finally, a human expert was invited to modify the care models for each synthetic patient.

Here, we would like to provide further details regarding the timestamp synthesis utilized in the EMERGE project. It is worth noting that the goal was to generate a population-frequency distribution of visits, rather than individual visit timestamps. To illustrate this strategy, let us consider an example where the EMERGE project has a real dataset of patients who visited the hospital for Viral Enteritis (ICD 008) before January 1st, and 100 such patients were generated. The EMERGE project first calculates the percentage of patients who returned to the hospital on January 2nd in the real dataset, let's say 10%. Based on this percentage, 10 visiting records will be generated for the synthetic dataset, and these records will be randomly assigned to the synthetic patient population.

The data-driven approach of EMERGE has been criticized for its potential risk of patient re-identification [5]. To address this issue, knowledge-based algorithms have been proposed [59, 69, 118]. The PADARSER [35] and CorMESR [90] methods combine expert knowledge and data-driven approaches by utilizing information from public statistics, Clinical Practice Guidelines (CPG), and Health Incidence Statistics (HIS). A toolkit called Synthea [147] provides a well-engineered implementation of PADARSER. The detailed development of the care model synthesis can be found in Fig. 2.

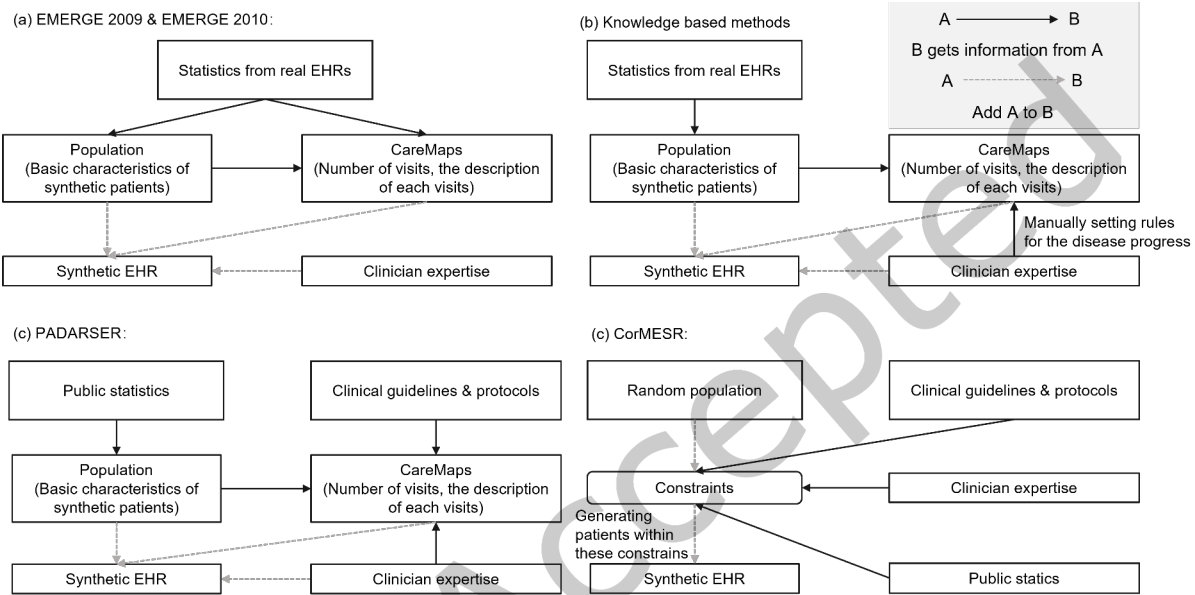


Fig. 2. A detailed development of the care model synthesis.

Unlike the methods discussed in sections 4 and 5, simulation-based algorithms do not necessarily require a reference dataset from the real-world. This reduces the risk of potential privacy breaches. However, these algorithms rely heavily on expert knowledge during the simulation of data generation mechanisms, leading to a significant increase in human workload. In the next section, we will introduce statistical modeling-based algorithms that do not require extensive manual guidance.

#### 4 STATISTICAL MODELING

This section will introduce data synthesis algorithms, as listed in Table 2, that utilize statistical modeling and sampling strategies. A common characteristic of these algorithms is their ability to approximate attribute distributions and synthesize data by sampling. Attribute distributions can be independent (as discussed in section 4.1), jointly attributed (using Copula functions, as discussed in section 4.1, or SMOTE, as discussed in section 4.2), conditionally distributed based on selected attributes (as discussed in section 4.3), or conditioned on attribute relations (as discussed in section 4.4). It should be noted that EHR simulation methods, as mentioned in section 3.2, may use statistical modeling in the synthesis pipeline; however, the performance of these methods relies more on prior knowledge, such as population information and treatment workflows of diseases, rather than sophisticated modeling of attribute distributions.

Table 2. Papers using single- and multi-variate distribution sampling. \*Although these papers did not report synthesis performance on medical data, they are open-sourced and easily implemented.

Paper reference	Year	Distributions	Medical data applications
[87]	2008	Multinomial sampling with a dirichlet prior	Demographics (Census data)
DPCopula [81]	2014	Copula functions with differential privacy	
DPSynthesizer [82]	2014	Copula functions with differential privacy	Demographics (Census data)
COCOA [6]	2016	11 common data distributions	NaN*
[60]	2016	Copula functions	Hospital emergency population
SyntheticDataVault [109]	2016	Copula functions	NaN*

We will denote the motivation as synthesized data  $Y = \{y_1^T, y_2^T, \dots, y_N^T | y_i^T \in \mathbb{R}^M, i \in [1, 2, \dots, N]\}$  from real data  $X = \{x_1^T, x_2^T, \dots, x_N^T | x_i \in \mathbb{R}^M, i \in [1, 2, \dots, N]\}$ . Here  $x_i^T$  and  $y_i^T$  are attributes for both datasets. For tabular data, the indexing of all  $N$  attributes is permutable. For a series of events, the indexing follows a chronological order, where  $i$  indicates the  $i$ -th events.

#### 4.1 Sampling from single- and multi-variate distributions

The simplest method for data generation is to generate each variable independently from the corresponding pre-defined distributions. These distributions can be denoted as  $Pr(X_i; \theta)$ , where  $\theta$  is the parameter estimated from the occurrence of values in the real-world datasets, and  $X_i$  is the  $i$ -th attribute.

This independent attribute distribution modeling has been widely used in many data-driven clinical applications, such as the EMERGE project [14, 93] we mentioned before. Gaussian distributions are used for continuous variables, and for discrete variables, Binomial distributions are used. However, the selections of distributions can be more varied. COCOA [6] is a framework for generating relational tables, and it has 11 common data distributions, including normal, beta, chi, chi-square, exponential (exp), gamma, geometric, logarithmic (log), Poisson, t-student (Tstu), and uniform (uni) [146].

The major limitation of this independent variable synthesis is that the intrinsic pattern between variables is discarded during training, leading to unmatched variables for synthetic populations. Thus, multivariate distributions of all attributes were proposed [87]. However, the multivariate distributions rely heavily on the type of distributions chosen, and for high-dimensional datasets, the computation efficiency is low, and the multivariate distributions might be sparse.

Copula functions provide a way to model the correlations between features, as well as avoid intensive parameter searching. For a two dimensional dataset  $X = \{x_1^T, x_2^T\}$ , and their marginal cumulative distribution function (CDF) of each attribute  $F_1(i) = Pr(x_1^T \leq i)$  and  $F_2(i) = Pr(x_2^T \leq i)$ . There exists a two-dimension Copula function  $C$  such that  $F(i_1, i_2) = C(F_1(i_1), F_2(i_2))$  [126]. Thus, the multivariate distribution modeling can then be simplified into Copula function estimating and marginal computation. The DPCopula [81] and its extension DPSynthesizer [82] used Gaussian copula functions, which further disentangled the multivariate Gaussian distributions into the product of the Gaussian dependence and margins.

The Copula functions have been proved to be efficient in population synthesis [60], i.e., generating basic demographics for the target population. An open-sourced Copula modeling implementation can be found in [109]. However, since the Copula is defined on the CDF, the Copula function-based modeling can only be applied to continuous variables.

## 4.2 A special multi-variate distribution modeling: SMOTE

The statistical methods described in subsection 4.1 explicitly compute the joint distributions of all variables, which can require a tricky parameter selection process. To avoid this, the Synthetic Minority Over-sampling Technique (SMOTE) [20] was proposed to generate samples through interpolation. In SMOTE, each piece of data from an individual is treated as a point in the data space, and the distribution of data is not explicitly modeled. SMOTE approximates the distribution by assuming that the data space can be spanned by all existing data points and samples from the distribution by interpolating existing data points. SMOTE is particularly useful for addressing data imbalance problems by creating data points that belong to the minority class.

A detailed SMOTE family review can be found in [43]. Being well-engineered and implemented in many toolkits [80], SMOTE and its variants has proved their efficiency in the medical data analysis domain, especially for disease classification where the number of patients is much less than the number of normal controls. Applications include Parkinson Disease classification [112], Alzheimer's Disease Classification [131], etc.

The SMOTE strategy considers all attributes together, while it fails to model the relations between attributes. Mathematically, considering  $x_1^T$  as the *label* vector for the combination of all other attributes, the synthetic samples in SMOTE only consider the conditional distribution  $Pr(x_{-1}^T | x_1^T)$ , rigidly inheriting the marginal of non-label attributes from real datasets by interpolation. Moreover, the interpolation nature of these methods is cursed with the mode collapse problem, where the synthetic data generated lacks diversity within the minority class.

## 4.3 Sampling from conditional distributions: multiple imputation

A further improvement for the attribute relation modeling is multiple imputation, shown in Table 3. Initially proposed for missing data imputation, the concept of multiple imputation proposed by Rubin [119] has also been widely used in privacy protection data releases. The main concept of multiple imputation is to produce partially synthetic datasets, where the missing attributes are predicted by other non-missing attributes. In the scenarios of privacy protection, the sensitive attributes are treated as "missing attributes": sensitive attributes are replaced by the values conditionally synthesized from non-sensitive attributes.

For example, let's consider dataset  $X = \{x_1^T, x_2^T, \dots, x_N^T\}$  with  $N$  attributes, and the subset  $X_C = \{x_1^T, x_2^T, \dots, x_C^T | C < N\}$  contains missing values (or sensitive values in privacy protection scenarios). The basic idea of multiple imputation is to sample each attribute  $x_i^T$  from conditional distributions  $\{x_i^T \sim P(x_i^T | x_1^T, x_2^T, \dots, x_N^T), i \in [1, C]\}$ , respectively. We will address all non-confidential (or non-missing) attributes as  $X_U = \{x_{C+1}, x_{C+2}, \dots, x_N\}$  for a clear statement.

The conditional distributions can be modeled explicitly with a specific mean and an variance. For example, General Additive Data Perturbation (GADP) [95] was proposed to define means and variances for the conditional distributions. Later in 2003, Information Preserving Statistical Obfuscation (IPSO) [15] was proposed. In the IPSO, the synthetic confidential attributes were obtained by multiple regression of  $X_C$  on non-confidential attributes  $X_U$ ; and this multiple regression model, also known as general linear model (GLM) has then been improved by regression trees [16] and fuzzy c-regression [18]. Thus, after IPSO, the multiple imputation algorithm using SVM [33] allowed the synthesis of discrete variables (but it can only be applied to discrete variables).

Multiple Imputation by Chained Equations (MICE) [152] also used regression models to synthesize sensitive attributes from nonsensitive attributes, but it is also featured by an iterative synthesis strategy, and the final synthesis results were pooled by all results synthesized during iterations. Applications can be found in breast cancer data synthesis [46].

Another extension of multiple imputation methods is to improve the privacy-protection during data release. The multiple imputation does not protect data privacy by nature. PeGS [107] then introduced the differential



Table 3. Papers using multiple imputation.

Paper reference	Year	Methods	Medical data applications
GADP [95]	1999	Defining mean and variances for the distributions of $X_C$ conditioned on $X_U$	NaN
IPSO [15]	2003	General linear models for $X_C$ from $X_U$	NaN
CART [16]	2010	Random forests for $X_C$ on $X_U$ (only applicable to discrete sensitive attributes)	Demographics (Census data)
[18]	2009	Fuzzy c-means for $X_C$ on $X_U$	Demographics (Census data)
[33]	2010	Support vector machines for $X_C$ on $X_U$	Health insurances data
[46]	2020	MICE	Cancer registry data from the Surveillance Epidemiology and End Results (SEER) program
PeGS [107]	2013	General linear models with differential privacy for $X_C$ from $X_U$ (only applicable to discrete sensitive attributes)	Public Patient Discharge Data from California Office of Statewide Health Planning and Development
PeGS applications [108]	2013	General linear models with differential privacy for $X_C$ from $X_U$ (only applicable to discrete sensitive attributes)	Public-use data files from Centers for Medicare and Medicaid Services

privacy concept in multiple imputation algorithms, and an application of their algorithm on healthcare data can be found in [108].

Multiple imputation algorithms modelled the condition of missing attributes (or sensitive attributes) on existing attributes (or all attributes). However, for fully synthetic data, one needs to traverse all variables to investigate the cross-conditional distributions, which is tedious and time-consuming.

#### 4.4 Sampling from conditional distributions with attribute relationships: Probabilistic Graphical Model (PGM)

To model the relations among attributes, a probabilistic graphical model (PGM) can be used. The edges for the PGM are relationships between attributes, while each node represents a conditional distribution of one attribute. A Bayesian Network, also known as a Bayesian belief network, is a graphical model that represents the joint probability distribution of variables of interest in a directed acyclic graph (DAG). The directions of the edges in the graph indicate causal relations between variables. Fig. 3 presents a popular healthcare Bayesian Network,

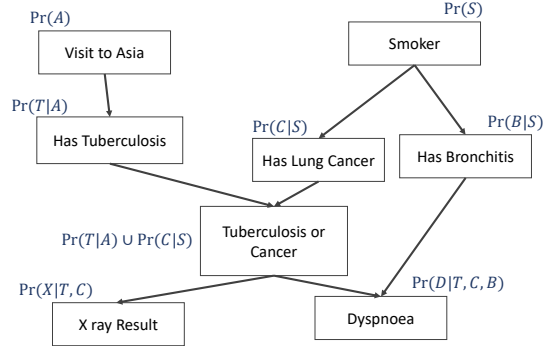


Fig. 3. An example for bayesian networks.

the Asia Network, which was defined in 1988 [77]. The Asia Network assumes a Bernoulli distribution for all attributes. To synthesize a patient's data from the Asia Network, one typically starts by sampling from  $Pr(S)$  and  $Pr(A)$  as the root nodes, and then obtains the values of other attributes from their conditional distributions, as shown in Fig. 3. Bayesian Networks can also be used to infer the conditional distributions of variables given other variables. In summary, Bayesian Networks provide a graphical representation of causal relations among variables and enable efficient calculation of the conditional distributions of each variable [77].

Three steps are required in order to use Bayesian Network to generate synthetic samples:

- First is structure learning, i.e., identifying the causal relations between attributes.
- Second is parameter learning, i.e., learning the conditional distribution of each variable.
- The third step is the inference: values of each attribute are first sampled from sets of initial attributes and propagated to values in other attributes according to conditional distributions.

It should be noted that the structure and parameter learning of Bayesian Networks can always be knowledge-driven, i.e., human experts can pre-define the relations between each attribute by their experiences. For data-driven algorithms, the structure and parameters are learned simultaneously. Data-driven methods for constructing a Bayesian Network include

- Constraint-based algorithms. In these algorithms, conditional independence tests were used to evaluate the dependency between each pair of attributes, and a BN was constructed using related attribute pairs.
- Score-based algorithms. The score-based algorithms first searched all possible structures, and then used a score function [75, 123] to evaluate these graphs.
- Hybrid algorithms. These algorithms used constraint-based algorithms to generate a subspace of all possible structures and then used score-based algorithms to evaluate and select these graphs.

We summarized all Bayesian Network-based algorithms in Table 4. Bayesian Networks have been widely used in medical data synthesis because the inherent suitability of Bayesian networks for knowledge-driven structure design and parameter learning enable improved trustworthiness of medical experts in this kind of models.

## 5 DEEP LEARNING

Two types of deep neural networks (also referred to as Deep Learning) have been widely used in data synthesis: Auto-Encoder (AE) [72] and generative adversarial networks (GAN) [49]. They are all composed of stacked linear or non-linear functions, and the major difference between these two types of methods is their target functions. An AE usually has two basic components, an encoder  $\mathcal{E}$  that maps vectors in the data space into a latent space, and a decoder  $\mathcal{D}$  that maps the latent space features into the data space. Mathematically, the objective function

Table 4. Bayesian Network-based algorithms for data synthesis. \*Although these papers did not report synthesis performance on medical data, they are open-sourced and easily implemented.

Paper ence	refer-	Year	Structural and parameter learning	Inference	Medical data applications
[134]		2015	Score-based (tabu search by Python Package bnlearn [137])	Global sampling	Demographics
PrivBayes [167]		2017	Constraint-based (Mutual In- formation and differential privacy)	Global sampling	NaN*
DataSynthesizer [111]	2017		PrivBayes	Global sampling	NaN*
[28]		2020	Score-based (AIC by Python Package pomegranate [122])	Global sampling	Demographics
[140]		2020	Constraint-based (FCI with EM for missing data)	Global sampling	CPRD Aurum data synthesis
[70]		2021	Score-based (by Python Package bnlearn [137])	Heart Disease (UCI), Dia- betes datasets (UCI), MIMIC- III	
[86]		2021	Constraint-based ( $G^2$ -test)	Global sampling from the la- bel attribute	Breast cancer (UCI), Dia- betes (UCI)
PrivSyn [168]		2021	Constraint-based (Indepen- dent Difference (InDif for short))	Gradually Update Method (GUM)	NaN*

for an AE with an input real data  $x$  is defined as

$$L(X, \mathcal{E}, \mathcal{D}) = \|\mathcal{D}(\mathcal{E}(x)) - x\|_p, \quad (1)$$

where  $\|\cdot\|_p$  is the p-norm. Synthetic data can be generated from AE by first sampling vectors from the latent space and then mapping the sampled vectors into the data space.

The GAN method, however, uses an additional network, discriminator, to optimize the performance of the data synthesizer. A GAN is also composed of two components: a generator  $\mathcal{G}$  and a discriminator  $\mathcal{D}$ . The inputs for generators are usually noises  $z$ , which are transformed into meaningful data vectors by deep learning models and can improve the variety of synthetic data. The inputs for the discriminator are both synthetic data from generators  $\mathcal{G}(z)$  and real data  $x$  for reference. The objective function of a GAN is

$$L(X, \mathcal{G}, \mathcal{D}) = E_x[\log(\mathcal{D}(x))] + E_z[\log(1 - \mathcal{D}(\mathcal{G}(z)))], \quad (2)$$

where  $E_x$  and  $E_z$  are expectations over all data instances. The generator can have many variants [4, 132], and some researches even use AE as an generator [135, 139], and the loss functions are then a combined value of both Eq. 1 and Eq. 2.

In this section, we categorize deep learning-based algorithms based on their target data types, considering the shared characteristics of AEs and GANs. While DP and fairness techniques are will be discussed separately to emphasize their unique capabilities. Additionally, we have included diagrams of these models to aid in understanding their structures, with red arrows highlighting inputs to the discriminator and gray boxes with blue boundaries representing the target synthesis object.

### 5.1 Deep neural networks for tabular data

According to the output of deep neural networks, we further divided the tabular data deep learning models into two categories: half synthesis networks whose target is to impute values, and fully synthesis networks.

**5.1.1 Half synthesis networks.** We plotted the structures of half synthesis networks in Fig. 4. A use case of AE in clinical data imputation can be found in [10]. Denoising autoencoders (DAE) [144] was proposed to extract robust feature representations, but its structure has also been used in missing data imputation. During training, the DAE first set several elements of inputs to zero randomly and then was trained to reconstruct the values of these elements. Once well-trained, the DAE could be used for missing data imputation. The objective function for DAE is the MSE between the corrupted input and the corresponding ground truth. Thus, the training of DAE is fully supervised and requires a large scale of complete ground truths. To improve the fully supervised training

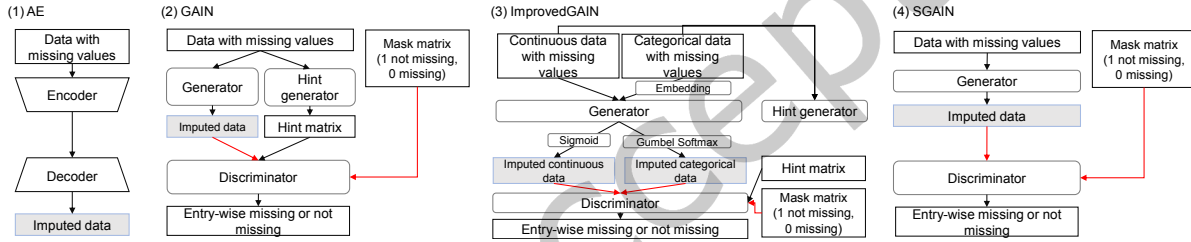


Fig. 4. Architectures for tabular data imputation.

of DAE, Generative Adversarial Imputation Nets (GAIN) [164] used a discriminator to optimize the synthesis performance during training. In data imputation tasks, the discriminators identify the real and fake elements in the imputed data. This imputation discriminator is similar to the patch discriminator [30] used in image synthesis. Instead of outputting a single binary value indicating whether the entire synthesized vector is real or fake, the discriminator produces a vector indicating the confidence of each value in the synthesized data. This "patch-wise" discriminator has been widely used in imputation GAN models.

The GAIN models were further improved by GAN training tricks such as Gradient Penalty and Wasserstein Loss in SGAIN [98]. To further specify the imputation of categorical and numerical missing variables, improved GAIN [17] split these two kinds into variables and imputes them separately.

**5.1.2 Fully synthesis networks.** For the fully synthesis networks, we will discuss these networks according to their architectures.

**Encoder-decoder or not: A debate on tabular data synthesis.** AE models, which are featured by the encoder-decoder structure, can be applied to tabular data synthesis. Synthetic data can be generated by manipulating the hidden feature vectors derived from real data. Examples can be found in AE-ELM [53] and OVAE [142], which used VAE to model the distributions of latent feature vectors.

As for the GAN models, we discovered a long-lasting debate over the object to be generated in the tabular GAN generators: some algorithms [21, 26, 127] used an encoder-decoder structure to map the original data into a latent space, while others generated the vectors of data directly [170]. We plotted their architectures in Fig. 5.

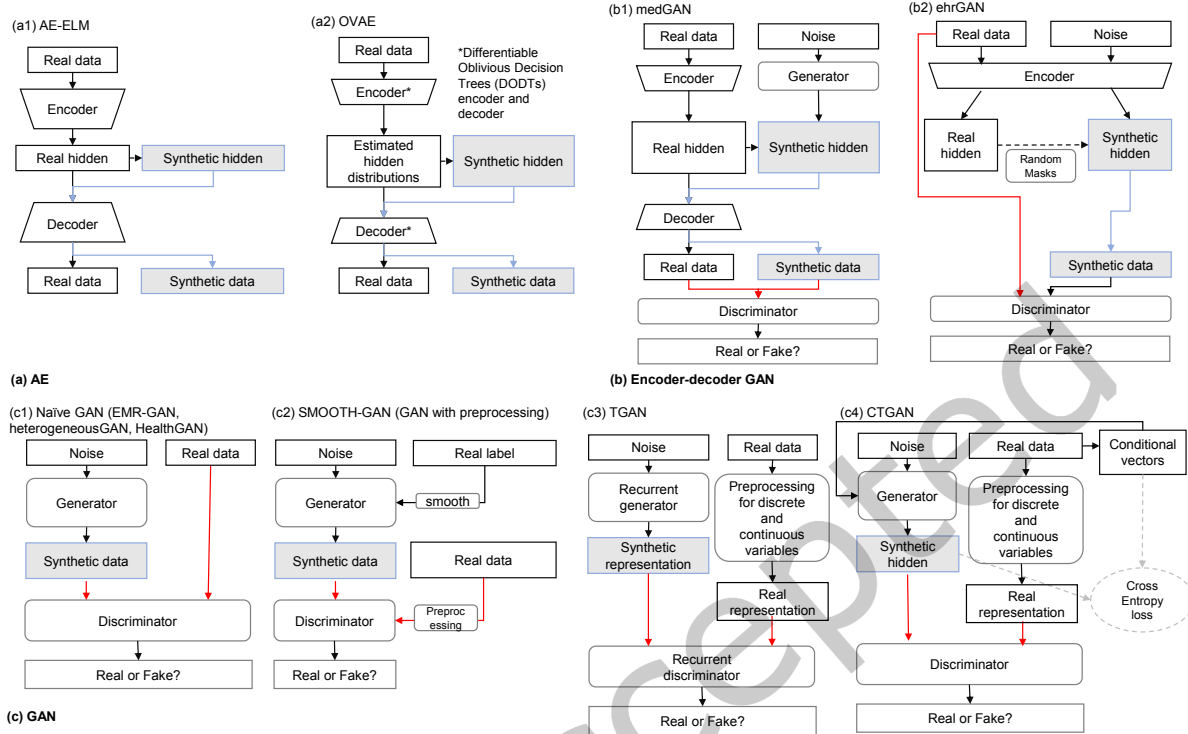


Fig. 5. Architectures for tabular data synthesis, grouped by the usage of an encoder-decoder structure.

Algorithms that used encoder-decoders to map feature vectors into a latent space tried to avoid synthesizing tabular data directly [21, 26]. For example, medGAN [26] used an encoder network that mapped the original values into a hidden space, and the generator generated values in the hidden space instead of in the original space. The encoder-decoder in medGAN was also pre-trained on real datasets, and the target for the pre-training was to reconstruct the input real datasets. EhrGAN [21] used the encoder-decoder structure to map a transition distribution of the form  $P(\tilde{x}|x)$ , where  $\tilde{x}$  and  $x$  are synthetic and real data.

However, EMR-GAN [170] has a conflicting conclusion claiming that the direct synthesis of values works better than the synthesis of hidden feature maps. They argue that because "these GANs (medGAN [26]) rely on an autoencoder, they may be led to a biased model because noise is introduced into the learning process". SPRINT-GAN [11], heterogeneousGAN [160], healthGAN [158] and SMOOTH-GAN [117] also synthesized data values directly.

TGAN [157] also discovered that "Simply normalizing numerical feature to  $[-1, 1]$  and using tanh activation to generate these (numerical) features does not work well". However, TGAN did not turn to latent space synthesis and did not use encoder-decoder structures. TGAN introduced a statistical representation synthesis strategy known as mode-specific normalization. Instead of synthesizing numerical values directly, the authors of TGAN used a Gaussian Mixture Model with  $m$  Gaussian distributions to model each feature, and they synthesized the parameters for GMMs. In their improved CTGAN [156], they replaced the LSTM generator in TGAN and used a conditional synthesis strategy to model the categorical features. Other pre-processing algorithms can be found at

smoothGAN [117], where continuous data were pre-processed by deleting outliers and scaling, and discrete data were mapped into continuous scores.

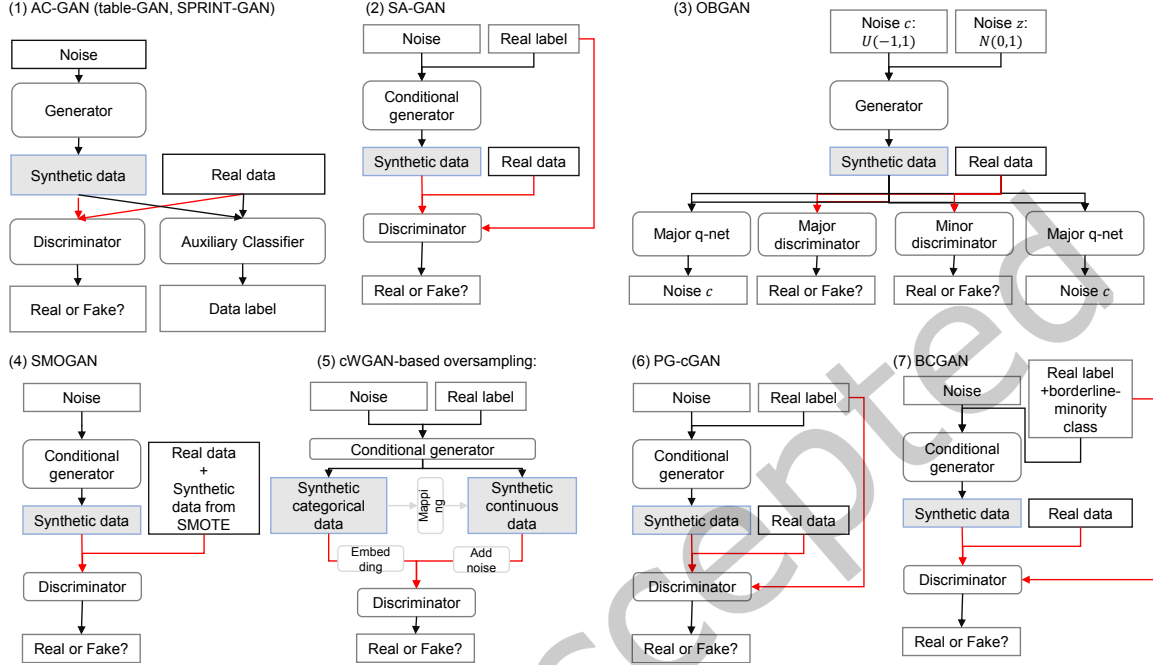


Fig. 6. Architectures of tabular data synthesis with labels.

**Synthesis with labels.** For downstream prediction tasks, the labels of data should be synthesized alongside the data. ACGAN [101] used an auxiliary classifier to synthesize data labels, and has successful implementations as SPRINT-GAN [11] and table-GAN [106].

Some medical data synthesis applications aim to synthesize data within a target group, e.g., synthesizing data with the minority class. For minority class data synthesis, the conditional generator has been widely used. BCGAN [130] and OBGAN [63] synthesized data points that were close to the decision boundary, and the former algorithm achieved borderline synthesis by introducing an additional borderline minority class; the latter used the Q-Net concept from InfoGAN [24], to allow output editing in GAN models. SMOGAN [76] used a SMOTE algorithm before GAN to augment the data points for GAN training. SAGAN [32] brought the relation between single attributes and data labels to GAN models. To better analyze discrete variables, cWGAN-based oversampling [38] adjusted the GAN model, and embedded the discrete attributes.

In addition to network architectures, different loss functions have also been introduced in deep generative models. ADS-GAN [162] introduced the indetifiability loss, which maximizes the Euclidean distance between real and synthetic data. HealthGAN adopted the Wasserstein loss [4] during the training of GAN models.

## 5.2 Deep neural networks for sequential data

For sequential data, recurrent structures have been utilized. The recurrent structures have many variants, such as Recurrent Neural Networks (RNN) [120], Gated Recurrent Unit [25] and Long Short-Term Memory (LSTM) [57], but they share a same basic structure shown in Fig. 7. Here, this recurrent mapping maps input  $\{x_1, x_2, \dots, x_T\}$

into an output  $\{y_1, y_2, \dots, y_T\}$ . Each cell in the recurrent mapping receives two inputs: one from the present  $x_T$ , and one from the latest past  $h_{T-1}$ . For the first cell, the  $h_0$  is addressed as the initial state, which, for many RNN implementations [115], are assigned by a vector of zeros. Each cell in the recurrent mapping outputs two outputs, but in some algorithms such as RNN and GRU,  $h_T = o_T$ .

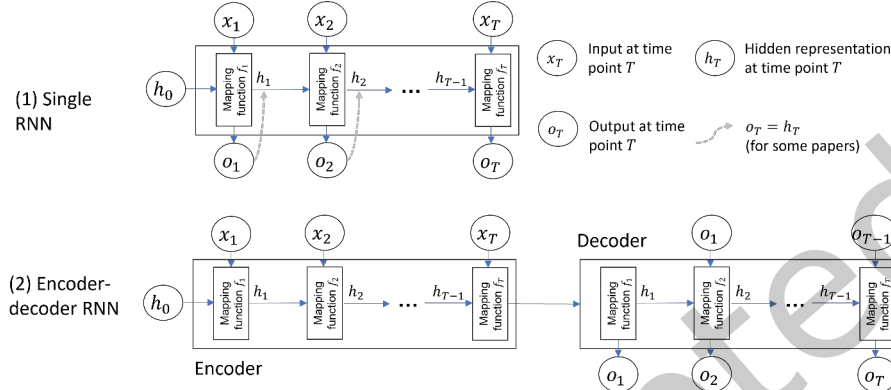


Fig. 7. Architecture of a recurrent network (1) and an encoder-decoder recurrent network (2).

**There is an implied convention of using encoder-decoder structures in sequential synthesis models [97].** As shown in Fig. 7, the encoder-decoder structure in sequential synthesis allows the network to read all time points before producing outputs. The decoupling of data reading and data generating has been commonly practiced in sequential data synthesis. Thus, we can easily find successful applications of encoder-decoder recurrent structures for sequential EHR generation, including TimeGAN [163], DAAE [78], LongGAN [135], and SynTEG [169], as is shown in Fig. 8.

However, some algorithms break this convention. We noticed that, in sequential EHR synthesis, RCGAN [40] and SC-GAN [148] generate data without the encoder-decoder structures. In addition, for ECG synthesis, we found another recurrent synthesis application without encoder-decoder structures [29]. These algorithms generate sequences directly from noises. However, these papers did not claim that their direct synthesis is better than latent synthesis.

Besides of recurrent networks, convolutional operations have also been used to investigate and preserve the inner correlations among time stamps, and papers including EVA [13] and CorGAN [139] used 1-D convolutions on temporal datasets. The experiments in ECG-GAN [29] also demonstrated the best synthesis performance using a recurrent generator and a non-recurrent discriminator. Despite the fact that they do not use recurrent structures, the EVA and CorGAN also decouple data reading and data generating with encoder-decoder structures.

Here, we would like to elaborate on loss functions improvements for sequential data synthesis. In addition to the network architectures, TimeGAN introduced a supervised loss in the training of recurrent GAN models, where the temporal relationships between time stamps were used for supervised criteria. The recurrent supervisor in TimeGAN was proposed to "explicitly encouraging the model to capture the stepwise conditional distributions in the data." Practically, TimeGAN used an additional recurrent network named supervisor. The recurrent supervisor received the latent feature extracted from the real data  $\{h_1, h_2, \dots, h_t\}$  (real hidden in Fig. 8), and outputted the latent features in the next time stamps  $\{h'_2, h'_3, \dots, h'_{t+1}\}$ . The loss function of the supervisor is thus

$$L_{\text{MSE}} = \sum_{i=0}^t \|h_i - h'_i\|^2. \quad (3)$$

This inner sequential supervision proved its efficacy in medical data synthesis using a large private lung cancer pathways dataset.

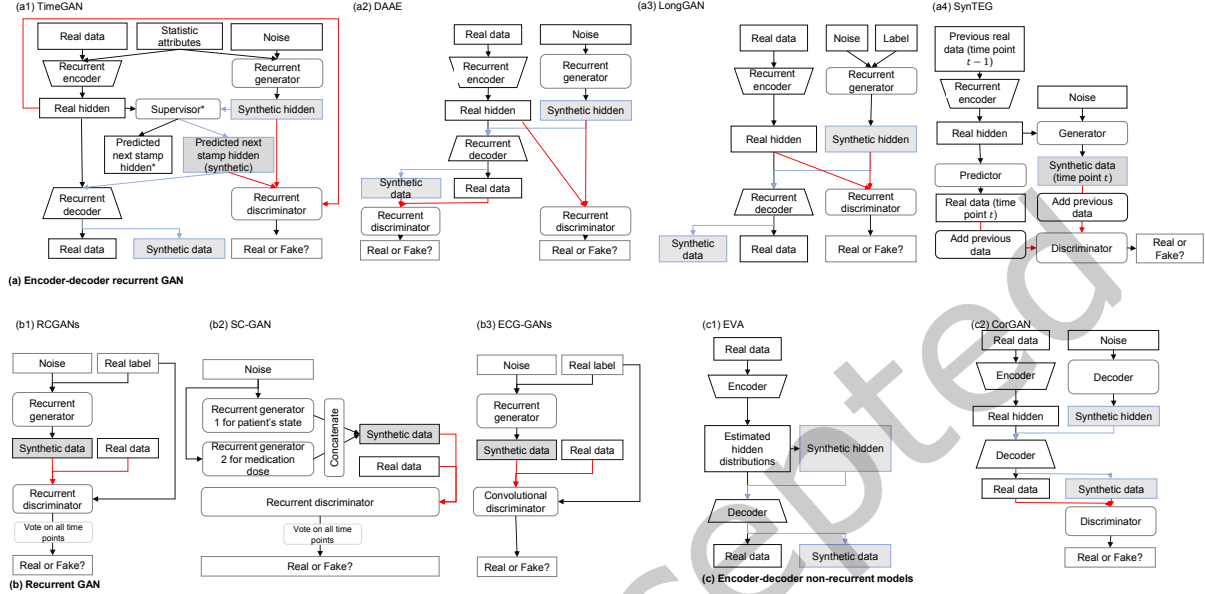


Fig. 8. Architectures of deep neural networks for sequential data, grouped by the use of encoder-decoder structure and recurrent structure. \*An additional MSE loss is added between real  $[0, t-1]$  and predicted next stamp hidden  $[1, t]$

### 5.3 Deep neural networks with additional targets

In this section, we will discuss deep neural networks with additional targets, such as differential privacy and fairness. The concept of differential privacy provides a well-defined solution to data privacy protection, and detailed definitions of differential privacy will be elaborated in section 6.3.3. To incorporate the concept of DP into deep learning algorithms, DP-SGD [1] was proposed in 2016, which adds noises in the gradient during training stages. In 2018, DPGAN [153] was introduced as the first GAN model incorporating differential privacy. It also adopts the noisy gradient strategy as in DP-SGD. DP-AuGM and DP-VAEGM [23] also use the DP-gradient descent strategy during training and propose to use AE- and VAE-based strategies for data synthesis.

PATE-GAN [67] incorporates the concept of differential privacy (DP) into GAN models by using a private aggregation of teacher ensembles (PATE) mechanism during the training of discriminators to synthesize data according to the level of DP. PATE-GAN uses  $n$  teacher discriminators and splits the real data into  $n$  subsets, with each teacher discriminator only discriminating between synthetic data and its corresponding subset of real data. Additionally, PATE-GAN implements a student discriminator that does not rely on any public data and only receives synthetic data as inputs, with the labels of these data assigned by the teacher discriminators. Successful applications of PATE-GAN include implementations on the Kaggle cervical cancer dataset [42], UCI ISOLET dataset [34], and UCI Epileptic Seizure Recognition dataset [34].

FairGAN [154] and FairGAN+ [155] aim to improve data fairness by using conditional GANs. In FairGAN, an additional discriminator is used to minimize attribute disclosure, i.e., to minimize the predictive ability of nonsensitive attributes on sensitive attributes. FairGAN+ then introduces classification fairness. We include



the architecture mentioned in this subsection in Fig. 9. Although fairness is an important quality required in a trustworthy training dataset, these fairness generative models have not yet been applied to healthcare data.

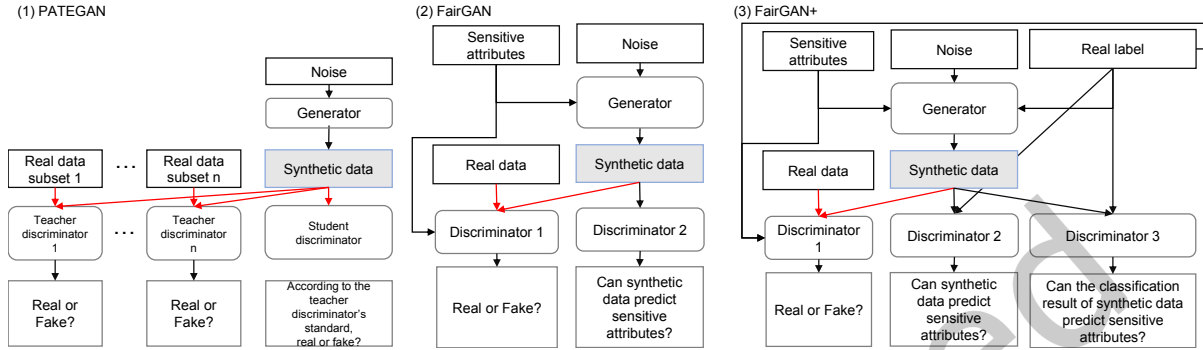


Fig. 9. Architectures of deep neural networks for differential privacy and fairness.

## 6 METRICS

We have categorized the evaluation metrics of the selected papers into four classes, as shown in Fig. 10. Importantly, the evaluation methods outlined in this are applicable to all data synthesis algorithms. These evaluation criteria are independent of the specific algorithm used and only require synthetic data and real reference data as input for assessment. All of these qualities contribute to the trustworthiness of the data. High-quality synthetic data is a key component of achieving trustworthy AI.

### 6.1 Fidelity

The fidelity of synthetic data can be evaluated by a panel of experts, such as clinicians who work closely with real data, who can inspect the synthetic data. For instance, SPRINT-GAN [11] employed ACGAN to generate a group of synthetic sequential health data, including blood pressure and medication counts, and then mixed real and synthetic patients. They invited three experienced physicians to determine whether the sequential data was real. EMERGE [93] invited a medical expert to review the synthetic healthcare records to identify any records that had content problems or inconsistencies, such as the disease category not matching the symptoms of synthetic patients. To help clinicians investigate data fidelity further, dimensionality reduction algorithms were used to visualize the data distribution. TimeGAN [163] used the T-SNE [56] algorithm to visualize the distributions of real and synthetic data points.

In addition to manual validation, the statistical closeness between real and synthetic data can also be quantitatively measured to assess synthesis performance. Statistical closeness can be measured in several ways:

**Statistical significance.** Two of the most commonly used textbook measurement of the similarity between two datasets in medical data synthesis are the Chi-squared test and the two-sample Kolmogorov–Smirnov (KS) test. The Chi-squared test is commonly used for discrete variables. In this test, a  $p$  value is obtained indicating the significance of the test, and commonly, a  $p > 0.05$  indicates that there is no significant difference between the real and synthetic variables [136]. On the other hand, in the KS test, the significance is measured under a specific confidence level, and each confidence level has a unique threshold for the statistic. One can claim that the synthetic data has similar distributions to the real data [88] if the statistic is lower than the threshold.

**Dimension-wise Probability.** The Kullback–Leibler (KL) divergence [73] can be used measure the distribution difference between real attributes and synthetic attributes. For discrete variables, the KL divergence from the

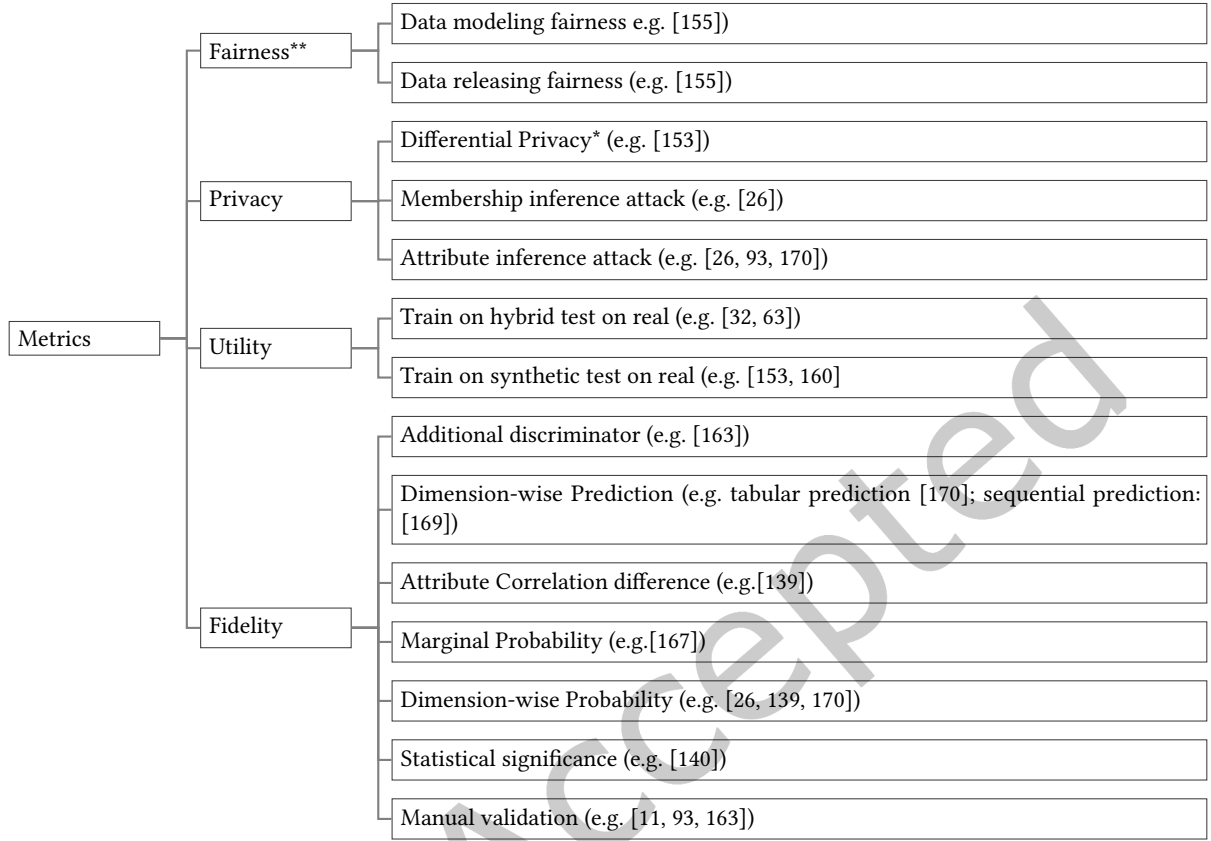


Fig. 10. Tree diagram of evaluation metrics. \*It should be noted that differential privacy is not strictly a metric by definition. \*\*Fairness is not commonly evaluated in medical data synthesis, while we still introduce this metric due to its high correlation with trustworthiness.

synthetic distribution  $Q$  to the real distribution  $P$  is defined as

$$D_{KL}(P||Q) = \sum_{x \in \mathcal{X}} P(x) \log\left(\frac{P(x)}{Q(x)}\right), \quad (4)$$

where the  $\mathcal{X}$  denotes all possible values in both datasets. For continuous variables, the KL divergence from  $Q$  to  $P$  is defined by a integral:

$$D_{KL}(P||Q) = \int_{-\infty}^{\infty} p(x) \log\left(\frac{p(x)}{q(x)}\right) dx, \quad (5)$$

where  $p$  and  $q$  are the probability densities of  $P$  and  $Q$ .

Specially for the ICD9 embedded EHR data, Bernoulli success possibility of each dimension can be used for a dimension-wise probability metric (an example can be found in CorGAN [139]). For each ICD9 code, the “success” in the Bernoulli trail is defined by the frequency of this code in all time points from all patients. The frequency for each ICD9 code should be similar between the real and the synthetic dataset.

**Marginal Probability.** Dimension-wise probability measures the distribution difference on individual attributes, while the marginal probability measures the joint probabilities among attributes. A  $k$ -way marginal is associated with a subset of  $k$  attributes. For example,  $Pr(x_1, x_2)$  is a 2-way marginal. The KL divergence can also be used to measure the difference in  $k$ -way marginal distributions. In PrivBayes [167], the total variation distance between the synthetic and real marginals is used to evaluate the marginal distribution. Mathematically, the total variation distance between the synthetic distribution  $Q$  and the real distribution  $P$  is calculated as

$$\mu(P, Q) = \sup_{\chi} |P - Q|, \quad (6)$$

where the supremum runs over all possible values or finite grids (for continuous variables) [113]. As with KL divergence, a lower distance indicates a better synthesis performance.

**Attribute Correlation difference.** The correlation between attributes is also an important feature of datasets. Preserving the correlation among attributes ensures the clinical utility of the synthetic dataset. To evaluate the preservation of feature correlation, TGAN [157] computed the mutual information between each pair of feature columns for single tables. Pearson's correlation [139] is another function that measures the intrinsic pattern among features. However, it does not provide a qualitative comparison of the correlation differences.

**Dimension-wise Prediction.** This evaluation also measures how well synthesis models capture the inner correlations in real datasets. Firstly, a random attribute  $x_{(k, real)}$  is selected from the real dataset, and the remaining attributes  $x_{(\neg k, real)}$  in the real dataset and corresponding synthetic data  $x_{(\neg k, syn)}$  are used to train two classifiers for predicting the value of the selected attribute. If the synthesis model captures the correlation between attributes well, then the performance of these two classifiers should be similar. In the case of sequential EHR data, the value for the last time point is often chosen as the target attribute [78].

**Additional discriminator.** Some articles [78, 163] introduced an additional discriminator to classify synthetic data from real data. Different from the discriminator in GAN models, this additional discriminator is not optimized alongside the generator. A lower accuracy of the additional discriminator indicates a better synthesis performance.

## 6.2 Utility

The utility of synthetic datasets is measured by the performance of synthetic datasets on downstream tasks. Usually, a label is assigned to each record in the datasets. For privacy preserved data synthesis, the Train on Synthetic Test on Real (TSTR) strategy has been widely used. A good synthetic dataset should achieve similar performance as the real dataset, and this classification similarity can be measured by KS tests. For data imputation and data augmentation, the utility is measured by classification improvement. The imputed data and augmented data should be able to improve the classification accuracy compared to the original dataset.

## 6.3 Privacy

Rubin proposed the use of fully synthetic data for privacy-preserved data sharing in 1993 [119]. However, it should be noted that synthetic data is not inherently private [66]. Therefore, if a "privacy-preserved" synthesis algorithm is proposed, it is recommended to conduct either an empirical analysis of privacy breach risks or an analytic proof of privacy. Of all the papers reviewed, three types of metrics have been used to evaluate the ability of privacy preservation, namely: 1) attribute inference attack, which involves obtaining specific values and statistical properties of the dataset; 2) membership inference attack, which aims to identify the presence of a specific record; and 3) differential privacy, which provides analytic proofs of privacy.

**6.3.1 Attribute inference attack.** The attribute inference attack assumes that the attacker has a compromised dataset (values of some non-sensitive attributes) and uses these attributes, along with the synthetic dataset, to speculate the sensitive attributes [89]. Most algorithms use a similarity attack strategy [26, 93, 170]. First, for each individual in the real dataset,  $n$  attributes are randomly chosen and provided to the attacker. Next, for each

record in the compromised dataset, the attacker computes the similarity of its publicized  $n$  attributes with all records in the synthetic dataset. The similarity measurements include mean absolute value difference and the Euclidean distance [15]. Finally, the attacker obtains the sensitive attributes of the most similar synthetic record as the values of sensitive attributes of this real individual.

Specifically, as most EHR synthesis relies on ICD9 codes, the data typically consists of discrete values. To preserve privacy, several studies [26, 93, 170] employed k-nearest neighbor classifications on the synthetic dataset for each sensitive attribute. By applying the classifiers on the compromised dataset, they could obtain the discrete values for the sensitive attributes. The classification accuracy metrics for each sensitive attribute were then reported, with lower accuracies indicating a higher level of privacy preservation.

**6.3.2 Membership inference attack.** The membership inference attack assumes that the attacker only has access to the data and not to the generative models. The attacker obtains a set of complete records where all attributes are publicized. By observing the synthetic dataset  $S$ , the attacker will determine whether a given data record in  $P$  was part of the synthetic model's training dataset [58]. Most membership inference attacks can be viewed as a classification task where the goal is to classify whether each record in  $P$  is 0 (not present in the training dataset) or 1 (present in the training dataset).

Most data generative models use a metric-based membership inference attack and perform it in an unsupervised manner. These attacks presume that synthetic records must bear similarities with the records that were used to generate them [22]. Using different distance metrics, the similarity between the target record  $p_i$  and all records from  $S$  can be measured. If the mean similarity between this record and all synthetic records is below a specific threshold, then this record is considered as 1 (presented in the training dataset). The metrics include Hamming distance (for discrete variables) [26] and the Euclidean distance (for continuous variables).

In 2017, a shadow model-based membership inference attack was proposed by Shokri et al. [124], which was later adapted for generative models by Stadler et al. [133]. For each record  $p_i$ , the shadow model attack trains two generative models: one with  $p_i$  and one without  $p_i$ . The synthetic records generated from the model trained with  $p_i$  are assigned the label 1, while the synthetic data from the model without  $p_i$  are assigned the label 0. Then, a classifier is trained on the synthetic records and their corresponding labels, and by inferring this classifier with the publicly available synthetic records  $S$ , the attacker can identify the presence of  $p_i$  in the training dataset.

**6.3.3 Differential Privacy (DP).** Differential privacy (DP) is an important solution in the context of membership inference. The term "differential" here refers to preserving patient privacy by tracking the difference between a released dataset and a modified version of it.

Suppose we have a dataset  $D$  with sensitive information about patients, including their age, gender, and medical conditions. The dataset contains four males. Now, suppose we add a new patient to the dataset, resulting in a new version called  $D'$ . If an attacker gains access to both versions of the dataset, they could easily figure out information about the new patient by comparing the two datasets. For example, they might notice that there is now one more male in the dataset, which could help them guess the new patient's medical condition. Differential Privacy (DP) aims to protect individual privacy in such situations by blurring the true values of the released data. In this case, DP would blur the gender information by adding random noise instead of revealing the exact number of males in the dataset.

Mathematically, assuming a function  $K$  where attackers can only obtain the information by applying  $K$  to  $D$ , the goal of DP is to minimize the difference between the distributions of  $K(D)$  and  $K(D')$ .

As mentioned previously, KL-Divergence is used to measure distribution differences. Since the concept of DP is to measure the maximum privacy breach, the maximum divergence is used in [37]. Thus, the target of DP algorithms can be mathematically defined as follows: an algorithm  $K$  provides  $\epsilon$ -differential privacy if the

maximum divergence between the distributions of  $K(D)$  and  $K(D')$  is bounded by  $\epsilon$ , i.e.,

$$Div_{\infty}(K(D)||K(D')) = \max_{d \in D} \left[ \ln \frac{Pr[K(D) \in S]}{Pr[K(D') \in S]} \right] \leq \epsilon. \quad (7)$$

More commonly, this definition is written as

$$Pr[K(D) \in S] \leq e^{\epsilon} Pr[K(D') \in S] \quad (8)$$

if  $K$  gives  $\epsilon$ -differential privacy. The DP can be achieved by adding specific patterns of noises when releasing the dataset, i.e.,

$$K(D) = D + \text{Noise}. \quad (9)$$

The distributions of noises include Laplacian mechanism [36] and the exponential mechanism [91]. For numerical data, the Laplacian mechanism outputs synthetic data with noises from a Laplacian distribution. For categorical data, the exponential mechanism introduces a scoring function, and produces the possibility of each value.

Unlike the two types of inference attacks mentioned before, differential privacy does not provide a typical “evaluation metric”, while it provides analytic proof of privacy in models, which means that DP can provide a guarantee for privacy protection. Thus, DP is, at most of the time, achieved by introducing the DP mechanisms into the synthesis algorithm. For example, Differentially Private Stochastic Gradient Descent (DP-SGD) [1] introduced the concept of DP in the SGD optimizer in deep learning; and [167] introduced DP in Bayesian Networks.

#### 6.4 Fairness

Fairness is a crucial aspect of trustworthy AI. A fair dataset should prevent exacerbating the differential impact among different groups, particularly among “protected groups” - a category of individuals protected by law, policy, or similar authority [125]. In the medical domain, fairness in datasets ensures equitable healthcare access and outcomes for people of different races and genders.

Considering the patients’ identities as sensitive attributes, a fair dataset [155] should accomplish two goals: 1) not reveal the sensitive attributes through insensitive attributes (data releasing fairness) and 2) avoid biased downstream predictions with respect to the sensitive attributes (data modeling fairness).

Considering a dataset composed of three components  $D = X_U, X_C, Y$ , where  $X_U, X_C, Y$  are insensitive attributes, sensitive attributes (race or sex), and data labeling, respectively. For data releasing fairness, two measurements can be used:

**Risk difference (RD) [155].** The RD for data releasing is defined by

$$RD_r = Pr(Y = 1|X_C = 1) - Pr(Y = 1|X_C = 0). \quad (10)$$

**Balanced error rate (BER) [41].** A trust model  $f : X_U \rightarrow X_C$  is built to predict sensitive variables  $X_C$  from insensitive variables  $X_U$  [41]. The balanced error rate (BER) of  $f$  is defined as

$$BER(f(X_U), X_C) = Pr[f(X_U) = 0|X_C = 1] + Pr[f(X_U) = 1|X_C = 0]. \quad (11)$$

According to BER, a synthetic dataset  $(X_U, X_C)$  is  $\epsilon$ -fair if for any trust models,

$$BER(f(X_U), X_C) > \epsilon \quad (12)$$

For the measurement of data modeling fairness, a classification model  $\eta : X_U \rightarrow Y$  is built to predict data labels  $Y$  from insensitive variables  $X_U$ . The data modeling fairness requires that the prediction of  $\eta$  is unbiased with respect to  $X_C$ . Mathematically, three metrics are defined to measure the data modeling fairness

**Risk difference (RD) [155].** The RD for modeling, which is also known as demographic parity, is defined by

$$RD_m = Pr(\eta(X_U) = 1|X_C = 1) - Pr(\eta(X_U) = 1|X_C = 0). \quad (13)$$

**Odds difference (OD)** [155]. The equality of odds requires the classifier to have equal true positive rates (TPR) and equal false positive rates (FPR) between two subgroups  $X_C = 1$  and  $X_C = 0$ . Mathematically, the odds difference is defined by

$$OD_m = \sum_{y \in \{0,1\}} Pr(\eta(X_U) = 1 | Y = y, X_C = 1) - Pr(\eta(X_U) = 1 | Y = y, X_C = 0). \quad (14)$$

## 7 COMMON PRE-PROCESSING PRACTICES AND DATASETS

In this section, we will provide common pre-processing practices for different data types [11], and we will also provide open-sourced datasets available for the synthesis algorithms development. The datasets we included in this survey are open-access for research purposes. However, due to the high sensitiveness of healthcare data, accesses to these dataset may require formal inquiries. In addition, we will also share three released synthetic datasets whose synthesis procedures produce hands-on experiences for data synthesis practitioners.

### (a) A single table

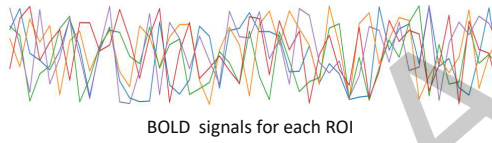
Patient Name	Sex	Age/Y	Temperature/°C	Smoking History
Ann	Female	27	37.8	Y
Mary	Female	20	NaN	N
Joe	Male	21	40.1	N
...	...	...	...	...

### (b) Relational tables

Patient Name	Sex	Age/Y
Ann	Female	27
Mary	Female	20
Joe	Male	21
...	...	...

Patient Name	Cancer Grade	Surgery	White cell count/ $10^9 \text{ml}^{-1}$
Ann	III	True	4.1
Joe	V	False	5.1
...	...	...	...

### (c) Medical Signals



Username	Device	Exercise	Time/min	Heart rate/ $\text{min}^{-1}$
Ann	Watch	Running	21	80
Ann	Watch	HIIT	10	NaN
Ann	Phone	HIIT	4	112
...	...	...	...	...

### (d) Time series of events

Patient Name	Sex	Age/Y	Smoking History	White cell count/ $10^9 \text{ml}^{-1}$	Force Vital Capacity/ml	X-ray grading	Medication	Dose
Ann	Female	27	Y	10.1	1700	Severe	NSAID	2

Time point 0: Patient admission      Time point 1: 1<sup>st</sup> laboratory test      Time point 2: 1<sup>st</sup> Medication      Time point 3: Patient Discharge

Fig. 11. Three major non-imaging medical data identified by this review paper: tabular data (a and b), medical signals (c) and time series of events (d).

Table 5. Open-sourced datasets used for non-imaging medical data synthesis.

Dataset name	Patient number	Data type	Data information	Disease Category
--------------	----------------	-----------	------------------	------------------

MIMIC-I (or 100 MIMIC) [94]		Medical signals and sequential EHR	Patient monitor data, patient-descriptive data (gender, age, record duration), symptoms, fluid balance, diagnoses, progress notes, medications, and laboratory results	Potential hemodynamically unstable
MIMIC-II [121]	33,000	Medical signals and sequential EHR	Patient monitor data, patient-descriptive data (demographics, admissions, transfers, discharge times, dates of death), diagnoses, notes, reports, procedure data, medications, fluid balances, and laboratory test data	diseases of the circulatory system; trauma; diseases of the digestive system; pulmonary diseases; infectious diseases; and neoplasms
MIMIC-III [65]	46,520	Medical signals and sequential EHR	Patient monitor data, patient-descriptive data, diagnoses, reports, notes, interventions, medications, and laboratory tests data.	Diseases of the circulatory system, pulmonary diseases, infectious and parasitic diseases, diseases of the digestive system, diseases of the genitourinary system, neoplasms, diseases of the genitourinary system, and trauma
MIMIC-IV [64]	383,220	Medical signals and sequential EHR	Hosp module contains patient-descriptive data, basic health data (blood pressure, height, weight...), medication, procedure data, and diagnoses. Icu module contains timing information data, patient monitor data, fluid balance, and procedure data.	Diseases of the circulatory system, pulmonary diseases, infectious and parasitic diseases, diseases of the digestive system, diseases of the genitourinary system, neoplasms, diseases of the genitourinary system, and trauma

eICU-CRD [114]	139,367	Sequential EHR	Vital signs, laboratory measurements, medications, APACHE components, care plan information, admission diagnosis, patient history, and time-stamped diagnoses.	pulmonary sepsis, acute myocardial infarction, cerebrovascular accident, congestive heart failure, renal sepsis, diabetic ketoacidosis, coronary artery bypass graft, atrial rhythm disturbance, cardiac arrest, and emphysema
Amsterdam UMCdb [138]	20,109	Medical signals and sequential EHR	Patient monitor and life support device data, laboratory measurements, clinical observation and scores, medical procedures and tasks, medication, fluid balance, diagnosis groups and clinical patient outcomes	Not specified
UT Physicians clinical database (UTP) [141]	5,501,776	Sequential EHR	Demographic data, vital signs, immunization data (body site, dose), laboratory data, transaction data (evaluation and management, radiology, medicine, surgery, anesthesia), appointment data, medications, and invoices	diabetes mellitus, hyperlipidemia, hypertension, and unspecified chest pain
Breast Cancer Wisconsin dataset (UCI) [34]	569	Tabular data	Diagnoses, radiuses, texture data, perimeters, areas, smoothness data, compactness data, concavity data, concave points data, symmetry data, and fractal dimensions.	Breast cancer
Heart Disease dataset (UCI) [34]	303	Tabular data	Demographic data, smoking status data, disease history data, exercise protocols, chart data (blood pressure, heart rate, ECG), pain status data, and diagnoses	Heart disease
Diabete dataset (UCI) [34]	70	Sequential data	Insulin dose, blood glucose measurement, hypoglycemic symptoms, meal ingestion, exercise activity	Diabete



### 7.1 Pre-processing methods for tabular data

For tabular data, each row of the table represents a patient, and columns of the table are features describing the patient. Tabular data is straightforward for data analysis, and the statistical properties, such as mean values and standard deviations, of the population can be derived. A sub-type of tabular data is multiple-tables, or relational tables, where information from different sites and under different levels is linked with one column from the tables. It should be noted that these relational tables can be merged into a meta table by a unique combination of linkage variables.

Tabular data are composed of two sets of variables, continuous variables and categorical variables. Continuous variables include age, blood pressure and temperature. In many statistical modeling-based algorithm, continuous variables are often pre-processed into discrete variables. It is because the finding a suitable prior distribution for continuous variables can be complex, and the joint or conditional distributions among multiple continuous variables are difficult to derive from data-driven methods. Thus, for most statistical modeling synthesis algorithms, continuous variables are classified into categorical variables according to their value. For example, in PrivBayes [167], continuous variables were first discretized into a fixed number  $l$  of equi-width bins and then binarized into  $\log l$  classes.

### 7.2 Pre-processing methods for sequential data

The sequential data majorly has two forms, the medical signals and the EHRs. Many datasets provide both data, while during synthesis and analysis, these two data forms have different pre-processing steps.

Medical signals include neurological signals such as EEG and fMRI, and physiological signals such as continuous blood pressure waveforms or continuous heart rates. For each time point, these signals only contain one value. These medical signals are often periodic, so pre-processing methods of these signals can focus on time domain [105, 129] and frequency domain [92]; and quantities such as amplitude [110] and frequency [100] for these signals are considered for the synthesis and analysis. To medical signals, pre-processing [12, 85] include de-noising, artifact removing, and normalizations. Specific procedures depend on the modality of medical signals.

Another sequential data form in the medical context is sequential events that collected in EHR. Although sequential events data could be technically merged into one meta table, with date stamps as an attribute, the tabular structure of the meta table fails to investigate the chronological order of events. Some sequential event synthesis algorithms, particularly the simulation-based algorithms [14, 35, 90, 93] in section 3, preserve the complex multi-table structure of EHR and the data structure is addressed as "patient care maps" or "careflow" in their algorithms. They would first synthesize several time points for each synthetic patient and then would add random tables for each time point. Each time point would have different numbers and types of tables, representing different events happened at this time point.

Other algorithms, however, normalize the events at each time point into a fix-size vector, because the fix-size input for each time point is required for algorithms, particularly the deep learning-based algorithms [26, 139, 169]. In these algorithms, the number of time points may vary, but the length of vectors at each time point must be fixed. Since all events contained in the datasets can span an event space, the fix-size vector is then a one-hot vector, and each entry of this vector represents the presence of the corresponding event at this specific time point. For example, considering an event space contains white cell abnormality, FVC abnormality, X-ray abnormality and medication usage, The fixed size vector  $[1, 1, 1, 0]$ , indicates a presence of white cell count abnormality, FVC abnormality and X-ray abnormality, while no presence of medication usage.

To standardize the event space and provide a standardized dictionary for different symptoms, many algorithms will first use International Classification of Diseases (ICD) format to describe the events, and then use the space of ICD codes to generate fix-size vectors for each time point. The ICD format [44] is a set of diagnostic encoding rules for clinical signs, symptoms, abnormal findings, complaints, social circumstances, and external causes of

injury or diseases. Under this format, two versions, ICD9 [44] and ICD10 [104], are commonly used in synthesis algorithms. By encoding each symptom into the ICD format, an attribute space containing all ICD codes in the dataset is constructed, and for each time stamp, a fix-size, one-hot encoded vector representing the coordinators in the ICD space is derived for each time stamp of EHR.

### 7.3 Synthetic datasets for EHR

We also discovered three released synthetic datasets, including Vanderbilt Synthetic Derivative (SD) dataset, Data Entrepreneurs' Synthetic Public Use File (DE-SynPUF) dataset and EMR Bots. These datasets, using different synthesis algorithms, provide hands-on practices for data synthesis.

**7.3.1 Vanderbilt Synthetic Derivative (SD) dataset.** The Vanderbilt SD dataset [27] is a synthetic dataset derived from a real database containing over 2.2 million patients. In SD dataset, demographic information, ICD-9 codes (diagnoses), CPT procedure codes, medications, vital signs, registry, patient histories, and lab values is included. The dataset was de-identified by altering the records with their closest neighbors.

**7.3.2 CMS 2008-2010 Data Entrepreneurs' Synthetic Public Use File (DE-SynPUF).** The DE-SynPUF dataset [103] is also a synthetic EHR dataset containing data from over 2 millions synthetic patients in five domains: Beneficiary Summary, which includes the demographic information and hospital enrollment reasons; Inpatient Claims, such as the presence of a surgery and other clinical measurements for patients admitted in hospitals; Outpatient Claims, which is the procedure of examinations happened outside of hospitals; Carrier Claims, which are derived of the bill information of all medical services, and include the name and date of the billed services, as well as the reimbursement amount related to this bill; Prescription Drug Events (PDE), which contains the medication information for each patient.

To derive this large synthetic dataset, a combination of simulations and multiple imputation algorithms were used. Five steps of data synthesis were used: 1) variable reduction, where only clinical useful attributes were selected to be released; 2) suppression, where the rare data that had disclosure risk were removed; 3) substitution, where, similar as SD dataset [27], the attribute values for each patient were replaced by its nearest neighbors; 4) imputation, where the collected values of single variables were replaced by values synthesized from conditional distributions on key variables; 5) perturbation, where timelines of patient records were altered by changing dates; 6) coarsening, where the continuous variables were coarsened into discrete variables.

**7.3.3 EMRBots.** The EMRBots [69] dataset is also an artificially generated EHR dataset contains three sub-datasets with 100, 10,000 and 100,000 synthetic patients. Unlike Vanderbilt SD and De-SynPUF dataset, the data from EMRBots are generated by a set of pre-defined criteria, which was set by an experienced clinician.

## 8 TAKEAWAY MESSAGES

### 8.1 A dilemma between data-driven and knowledge driven approaches

Deep neural networks have been providing efficient tools in medical image synthesis. In the field of non-imaging data synthesis, deep generative models are also on the top of our recommendation list. Deep neural networks, such as CTGAN [156], medGAN [26] and temporal gans such as TimeGAN [163], are easy to implement, and they do not require any prior knowledge during the training. However, the data-driven nature of deep generative models makes these methods suffer from overfitting (or mode collapse in data synthesis field). Methods such as Wasserstein loss [4], ease the pain of overfitting. Moreover, deep generative models are notorious for their difficulty in interpretation. If there are any unreal output values, it is nearly impossible for ones to adjust accordingly in deep generative models. Attention mechanisms [7, 143] have been widely used to improve the network explainability, while they have been rarely discussed in the non-imaging data synthesis field.

The EMERGE family [35, 93] and Bayesian Networks [167] allow ones to bring experts' prior knowledge in data synthesis. However, both of these algorithms are not good at handling high-dimensional data (tabular data with >1000 attributes) [167]. For EMERGE-based methods, building patients' caremap models from scratch is laborious and time-consuming. Synthea [147] provides over 35 modules for different patient caremap modeling regarding different diseases, while customized caremap modeling is still difficult. A new type of data modeling named theory-driven modeling [68] is proposed to find a balance between knowledge-driven and data-driven methods. In addition, incorporating prior knowledge into deep generative networks [116] shall be a potential solution towards the synthesis efficiency and network explainability.

## 8.2 A dilemma between data utility and data privacy

In 2021, a comparative study [133] was performed on different data synthesis algorithms, and the authors evaluated the risk of privacy violation and the utility of synthetic data from these algorithms. They discover that synthetic data does not protect the patients' privacy naturally. The synthetic data with high utility is vulnerable to the membership inference attack, thus, has a high risk of individual re-identification. Meanwhile, they also perform a utility assessment on DP-based generative models and the results further support the dilemma between data utility and data privacy.

This dilemma is also reported in many articles in this review, especially those with DP mechanism [23, 153, 167]. With more noise added (lower  $\epsilon$  in DP), the statistical closeness and prediction accuracy for downstream tasks get lower. Thus, it is important to re-think the rationale of **only** using data synthesis to protect privacy during data release. In 2004, a paper [2] was proposed to combine three approaches for confidential data release: (1) synthetic data releasing; (2) real analytical data releasing and (3) restricted access to data. This complex method combining techniques and policy might be a solution to this dilemma, yet research investigating this dilemma is still ongoing.

## 8.3 Beyond the debate over encoder-decoder: uncertainty and diversity

For tabular data, where rows represent individuals and columns represent attributes, various deep learning architectures have been proposed. In section 5.1.2, a debate was presented regarding the use of encoder-decoder structures in tabular data synthesis. Some algorithms [11, 158, 170] synthesize data directly, while others [21, 26] synthesize and sampling in a latent space and use a decoder to generate target data from the latent space. While we cannot determine a clear winner in terms of synthesis performance in this review, we can provide two perspectives that will help readers evaluate these two synthesis strategies.

First is the uncertainty of the synthetic data. The encoder-decoder approach aims to reconstruct the input as accurately as possible, but even with a well-trained model, the mean squared error (MSE) loss between the input and the reconstruction can never reach zero. This means that there will always be some additional noise in the synthetic data, which can increase uncertainty and potentially introduce a shift between the synthetic and real data domains.

Second is the diversity, where latent space synthesis has its own advantages. For instance, energy-based models [74] introduce a new perspective that allows us to understand the diversities of data in GAN models. Additionally, these models provide theoretical proof for the diversities in the latent space synthesis.

## 8.4 Other potential research directions

In addition to investigating the solutions to two aforementioned dilemmas, we will provide other potential research directions for non-imaging data synthesis in this subsection.

**New models and new metrics.** Diffusion models have shown superior synthesis performance compared to GANs in the domain of image synthesis [31]. Although some studies, such as [52, 165], have explored the potential of diffusion models in non-imaging data synthesis, further research in this area is still relatively scarce.

As for the metrics, we noticed that fairness is not commonly evaluated in medical data synthesis even though this metric has a high correlation with trustworthiness. Additional metrics related to privacy, including  $k$ -anonymity,  $l$ -diversity,  $t$ -closeness and  $p$ -indistinguishability [89] are also not commonly practiced in the data synthesis field, and implementations of these metrics have not been investigated yet.

**Multi-modality synthesis.** The concept of multi-modality [166] is widely used in medical image synthesis, where different image modalities such as CT, MRI and X-ray images are synthesized together for a comprehensive representation of patients. Since non-imaging medical data is also an important clinical modality, the hybrid synthesis of imaging and non-imaging data should be considered. However, many algorithms only investigate the independent synthesis of imaging data and non-imaging data and coupled synthesis is still scarce in the literature.

**Data harmonization using data synthesis.** Data collection in healthcare research involves gathering data from various sources, each with its own unique formats and properties. Non-imaging data synthesis algorithms offer a solution by generating synthetic data that follows a standardized format while retaining the statistical characteristics of the original data sources. Despite this potential, the application of non-imaging data synthesis algorithms in data harmonization has not received adequate attention in the development of non-imaging data. Therefore, this section aims to highlight the potential of non-imaging data synthesis algorithms in achieving data harmonization, thereby contributing to the overall improvement in the reliability of AI applications.

## 9 CONCLUSION

The trustworthiness represents a set of essential qualities required for an AI algorithm: privacy, robustness, explainability, and fairness. In order to develop the trustworthy AI on non-imaging medical data, data synthesis algorithms have been proposed. By improving the number, variety and privacy of training samples, data synthesis algorithms are able to help AI models with a better accuracy at a lower cost. Trustworthy AI algorithms should cover all tasks in the AI field, including prediction and generation. However, most works so far concentrate on trustworthy “predictive modeling”, whereas the AI generation model raises many concerns as those exposed in this manuscript. Thus, this survey aims to be a referential point of discussion and a motivating catalyst of research around trustworthy synthetic data generation.

In this paper, we identified three major types of non-imaging medical data synthesis algorithms and provided a comprehensive literature review about them and their evaluations. We also identified two challenges faced by all data synthesis algorithms: finding the balance between the utilization of data and knowledge and finding the balance between data utility and data privacy. We revealed some limitations existing in non-imaging data synthesis, and called for new architectures, new evaluation metrics and multi-modality strategies to drive future efforts in this exciting research area.

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